THE CHEMICAL COMPOSITION

OF

ENVIRONMENTAL TOBACCO SMOKE:

SOME COMMENTS

ON

THE OCCUPATIONAL SAFETY

AND

HEALTH ADMINISTRATION'S NOTICE

ON

'INDOOR AIR QUALITY'

(OSHA, 1994)

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About the author:

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General:

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1928: Moved to Toronto, Ontario, Canada

1942-1945: Served in Royal Canadian Navy (North Atlantic)

1954: Moved from Toronto, Ontario, Canada to Winston-Salem NC

1961: Naturalized American citizen

Education:

Received B.A. (Honors Chemistry) at University of Toronto

Received M.A. in Organic Chemistry, University of Toronto

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Advisor for B.A., M.A., and Ph. D. theses was Dr. George F Wright, Professor of Organic Chemistry[1].

Eleven publications[2] jointly with Dr. Wright on the topics of the three theses.

Cancer Research:

1947-1952: Research Assistant, Banting and Best Department of Medical Research, University of Toronto

1952-1953: Research Associate, Banting and Best Department of Medical Research, University of Toronto

From 1947 to 1953 worked full time each year from May till September at the Banting Institute; worked part-time (weekends) from September through May during school year.

[1] Dr. George F Wright was a long-time collaborator with Dr. E. L. Wynder on the composition of tobacco smoke. He preceded Dr. Dietrich Hoffmann as the chemist working with Dr. Wynder's group at the Sloan Kettering Institute. Drs. Wright and Wynder were coauthors on ten publications dealing with tobacco smoke components and their precursors in tobacco.

[2] Examples include:

- McKenzie JCJ, Rodgman A, and Wright GF (1952), Diels-Alder Additions with Dialkyl Azodicarboxylates and Azo-*bis*-formamidine. J. ORG. CHEM. *17:* 1666-1674.
- Rodgman A and Wright GF (1953), Methods for Acceleration of a Typical Diels-Alder Reaction. J. ORG. CHEM. *18:* 465-484.
- Brook AG, Rodgman A, and Wright GF (1952), Oxymercuration of 2,6-Dimethylhepten-5-ol-2. J. ORG. CHEM. *17:* 988-999.
- Rodgman A and Wright GF (1953), The Kinetics of Alkene Mercuration. J. ORG. CHEM. *18:* 1617-1631.
- McNeely KH, Rodgman A, and Wright GF (1955), Oxymercuration of Bridged Cycloölefins. J. ORG. CHEM. *20:* 714-725.
- Rodgman A, Shearer DA, and Wright GF (1957), Reversibility of Alkene Oxymercuration. CAN. J. CHEM. *35:* 1377-1383.
- Berg OW, Lay WP, Rodgman A, and Wright GF (1958), Deoxymercuration. CAN. J. CHEM. *36:* 358-370.
- Abercrombie MJ, Rodgman A, Barucha KR, and Wright GF (1959), Mechanisms of Oxymercuration. CAN. J. CHEM. *37:* 1328-1359.

1953-1954: Research Associate, Banting and Best Department of Medical Research, University of Toronto

Research Director (1947-1954) at Banting and Best Department of Medical Research was Dr. W. R. Franks, Cancer Research Professor. Areas of research included carcinogenesis of polycyclic aromatic hydrocarbons and nitrogen mustards, anticarcinogenesis, and chemoantigens.

Six publications[3] jointly with Dr. Franks on chemical carcinogenesis.

Tobacco and Tobacco Smoke Research:

1954-1965: Senior Research Chemist, R&D Department, R. J. Reynolds Tobacco Company, Winston-Salem NC (RJRT R&D)

1965-1972: Head, Smoke Composition Section, RJRT R&D

1973: Acting Manager, Chemical Research Division, RJRT R&D

1974-1975: Head, Smoke Composition Section, RJRT R&D

1975-1976: Manager, Analytical Research Division, RJRT R&D

1976-1980: Director of Research, RJRT R&D

1980-1987: Director of Fundamental Research, RJRT R&D

1987- : Consultant

About 40 presentations and publications[4] on the composition of tobacco smoke; several patents

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[3] Examples include:

- Franks WR, Rodgman A, and Brown WK (1948), Chemoantigens and Carcinogenesis. ANN. RPT., ONTARIO CANCER TREATMENT & RESEARCH FOUNDATION: 53-54.
- Franks WR, Manser J, and Rodgman A (1949), Synthesis and Testing of Anticarcinogens Including Chemoantigens. ANN. RPT., ONTARIO CANCER TREATMENT & RESEARCH FOUNDATION: 75-77.
- Rodgman A and Franks WR (1952), Reaction of Thyroxine with Aromatic Isocyanates. J. AM. CHEM. SOC. *74:* 6296-6297.

[4] Examples include:

- Rodgman A (1959), The Composition of Cigarette Smoke. III. Phytadienes. J. ORG. CHEM. *24:* 1916-1924.
- Rodgman A and Cook LC (1960), The Composition of Cigarette Smoke. IV. α-Tocopherol. TOB. SCI. *4:* 7-8.
- Rodgman A, Cook LC, and Mims SS (1961), The Composition of Cigarette Smoke. V. Solanesenes. J. ORG. CHEM. *26:* 497-501.
- Rodgman A, Cook LC, Bellin SA, Mims SS, and Young GW (1962), The Composition of Cigarette Smoke. IX. The Composition of an Aliphatic Ester Fraction from Tobacco and Tobacco Smoke. TOB. SCI. *6:* 42-49.
- Rodgman A and Cook LC (1962), The Composition of Cigarette Smoke. XI. Heterocyclic Nitrogen Compounds from Turkish Tobacco Smoke. TOB. SCI. *6:* 176-179.
- Rowland RL, Rodgman A, Schumacher JN, Roberts DL, Cook LC, and Walker WE Jr (1964), Macrocyclic Diterpene Hydroxyethers from Tobacco and Cigarette Smoke. J. ORG. CHEM. *29:* 16-21.
- Cook LC and Rodgman A (1965), The Composition of Cigarette Smoke. XIV. Hexahydrofarnesyl Acetone (Phytone) and 2-Methyl-5-isopropyl-1,3-nonadien-8-one (Solanone) from Turkish Tobacco Smoke. TOB. SCI. *9:* 137-139.
- Rodgman A (1984), Symposium Chairman's Introduction and Summary to 38th Tobacco Chemists' Research Conference Symposium on *Design of Low-"Tar" Cigarettes*. RECENT ADV. TOB. SCI. *10:* 1-3, 151-159.
- Rodgman A (1991), *A Comparison of the Chemical and Physical Properties of Cigarette Mainstream Smoke (MS), Cigarette Sidestream Smoke (SS), and Environmental Tobacco Smoke (ETS).* Document submitted to the Environmental Protection Agency, December 1991. Revised copy provided EPA, July 1992.
- Rodgman A (1992), Environmental Tobacco Smoke. REGUL. TOXICOL. PHARMACOL. *16:* 223-244.

on control of the composition of cigarette smoke.

Professional Societies:

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Profession-Related Activities:

1951-1954: Lecturer in four courses [Organic Chemistry (2), Physical Chemistry, Mathematics for Chemists] sponsored by the Chemical Institute of Canada, Toronto, Ontario, Canada for chemical technicians.

1956-1962: RJRT Representative, Industry Technical Committee, Council for Tobacco Research (USA)

1963-1965: Member, Editorial Board, *Tobacco Science*

1965-1967: Vice Chairman, Editorial Board, *Tobacco Science*

1974-1976: Program Editorial Committee, Tobacco Chemists' Research Conference (Chairman, 1976)

1969-1976: Auditor, Tobacco Working Group, National Cancer Institute Smoking and Health Program (Toward Less Hazardous Cigarettes)

1976-1978: Member, Tobacco Working Group, National Cancer Institute Smoking and Health Program (Toward Less Hazardous Cigarettes)

1978-1987: Member, Editorial Board, *Beitrage zur Tabakforschung International*

1984-1987: Member, Technical Study Group, Cigarette Safety Act of 1984

THE CHEMICAL COMPOSITION OF ENVIRONMENTAL TOBACCO SMOKE: SOME COMMENTS ON THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION'S NOTICE ON 'INDOOR AIR QUALITY' (OSHA, 1994)

SUMMARY

- **ETS Exposure Is Immensely Different from Exposure to MS during Active Smoking**

Despite the fact that throughout its report OSHA acknowledges the profound differences among MS, SS, and ETS, it repeatedly and erroneously equates the chemical, physical, and biological properties of ETS to those of MS and/or SS.

ETS is neither MS or SS.

Chemically, MS, SS, and ETS are qualitatively the same but quantitatively different; physically, they differ significantly.

ETS comprises *diluted* and *aged* exhaled MS plus *diluted* and *aged* SS generated during the puff and during the smolder period between puffs.

The compositions of MS, SS, and ETS are qualitatively similar but quantitatively different, *i.e.*, the components (about 4,800) identified to date in MS could eventually, with enough time and effort, be identified in SS and ETS. For MS, identified components predominately in the particulate phase (PP) number about 4,100; in the vapor phase (VP), about 1,000. For some components, measurable amounts occur in both phases.

The phase distribution of components between vapor and particles is different for MS, SS, and ETS. This is caused by evaporative losses due to the dilution of SS and the high dilution of ETS. An additional factor is the difference between the pH of MS (< 7.0) and the pH of SS (> 7.0) and ETS. *E.g.*, in the acidic MS (pH < 7.0), nicotine is protonated and mainly ($> 99.9\%$) in the MS PP; whereas, in the usually alkaline SS (pH > 7.0), nicotine is nonprotonated, *i.e.*, "free," and is mainly in the SS VP. More than 95% of the nicotine in ETS is nonprotonated and in the VP.

Particles of freshly generated MS increase in size in the smoker's respiratory tract because of coagulation and water acquisition in the nearly 100% relative humidity atmosphere of the respiratory tract. On exhalation, these enlarged particles (20 to 25% larger than the inhaled particles) almost immediately lose water and other volatile components to the atmosphere by evaporation. As a result, their size decreases. Similarly, freshly generated SS particles — originally about the same size as freshly generated MS particles — also lose volatile components, including nicotine, to the atmosphere and diminish in size. Eventually, the mass mean aerodynamic diameter (MMAD) of the exhaled MS and the SS particles formed during smolder is reduced 40 to 50% through these evaporative processes. Percentage retention, as measured by weight loss, of these smaller particles — now almost devoid of highly volatile components — is much less than that for the volatile component-rich MS particles during active smoking. Measurements in active smokers have given % MS PP retentions ranging from 50 to 90%; theoretically, retention of ETS PP should range from 10 to 20%. When measured with experimentally generated ETS smoke particles in a 1982 study, retention was found to be 11%. In a 1994 study where deposition fractions reported were for lower MMAD smoke particles than those in the 1982 study (0.14 μm *vs* 0.41 μm), higher retention values were reported for males exposed to low and high levels of *aged and diluted SS* and females exposed to the higher smoke level. For males, retentions were 36 and 41% for low and high exposure rate, respectively, and were independent of the analytical method (UV or by solanesol retention). For females

(high level exposure only), the retention was not only significantly lower than in the male case but also different for the two analyses: 17% (UV), 27% (solanesol).

- **None of the Components in the "Lists of 43" Has Been Shown to Be A Human Lung Carcinogen**

In their efforts to define ETS as carcinogenic, OSHA (and EPA) relied on lists of MS (and tobacco) components defined as "tumorigenic" or "carcinogenic." The two lists differ. The OSHA list, comprising 43 components[a], was developed within OSHA; the EPA list, comprising 43 components, was originally assembled by Hoffmann and Hecht (1990) from IARC data. A total of 50 MS (and tobacco) components appears on the two lists; 35 components appear on both lists (**Tables 4** and **5**).

In their reliance on these lists (**Table 4**), both agencies have disregarded (i) the nature of the experimental evidence on which the defined "tumorigenicity" or "carcinogenicity" was based and (ii) whether any or all of the components listed by OSHA and EPA really belong on such a list.

Between them, OSHA and EPA (via Hoffmann and Hecht) have listed 13 PAHs in tobacco smoke as significant tumorigens. Both OSHA and EPA apparently accept the tumorigenicity of these PAHs despite the fact that almost every claim over the past four decades pertinent to or against PAHs, including BaP, in tobacco smoke has been demonstrated to be incorrect. In some instances, data proving the incorrectness of the claims were provided by the original claimants, some of whom apparently have forgotten the significance of their own findings. Examples of claims against PAHs in tobacco smoke that have been demonstrated to be incorrect include:

- PAHs in cigarette MS arise from the lighting source (matches, solvent-charged lighters).
- PAHs in cigarette MS arise from tobacco leaves contaminated with PAH-containing air pollutants.
- Major source of PAHs in cigarette MS is the cigarette paper.
- Major precursor of PAHs in cigarette MS is the cellulose in the tobacco.
- Major precursor of PAHs in cigarette MS is the saturated aliphatic hydrocarbons in the tobacco.
- Fate of an individual tobacco component on pyrolysis in an experimental situation is identical with its fate in the multicomponent tobacco matrix during the cigarette smoking process.
- Major mechanism of PAH formation during the smoking process involves tobacco component fragmentation followed by recombination of the fragments.
- Major mechanism of PAH formation during the smoking process involves unimolecular reactions.
- BaP level in CSC is an "indicator" of the levels of other PAHs with four or more rings.
- BaP level in CSC is an "indicator" of the tumorigenicity of CSC to the skin of laboratory animals.
- Phenol level is an "indicator" of the level of promoting phenols which will enhance the biological effect of PAHs as measured in skin-painting experiments.
- It is highly unlikely that alkylated and polyalkylated PAHs, *e.g.*, methyl-, dimethyl-, or trimethylbenz[*a*]anthracenes, will be present in tobacco smoke.
- It is highly unlikely that cyclopentabenz[*a*]anthracenes will be present in tobacco smoke.

[a] The title of Table II-2 (OSHA, 1994) claims *43 Chemical Compounds Identified in Tobacco Smoke for Which There Is "Sufficient Evidence" of Carcinogenicity in Humans or Animals* but only 42 components are listed.

- Selective filtration of components involved in the tumorigenicity of MS is an "impossibility."

During the past four decades, numerous authorities and scientific groups — many of them anti-tobacco smoking — have repeatedly stated that no individual MS component or class of MS components acting individually or in concert at the levels found in MS can account for the biological effects observed in laboratory animals treated with MS by inhalation or with MS condensate (CSC) in rodent skin-painting experiments).

Only five components {benzo[*a*]pyrene (BaP), *N*-nitrosodimethylamine (NDMA), *N*-nitrosodiethylamine (NDEA), cadmium, polonium-210} on the two lists have been tested experimentally (**Table 4**) for tumorigenicity to lung tissue by exposure of laboratory animals via inhalation. The results with BaP, NDMA, and NDEA, tested in inhalation studies at dose levels substantially exceeding those in MS, were rated "equivocal" by the Registry of Toxic Effects of Chemical Substances (RTECS, 1986). Cadmium and polonium-210 administered to rats at massive dose levels produced lung tumors similar to the tumor type associated statistically with cigarette smoking. However, the Surgeon General, in several of his annual reports (USPHS, 1981, 1982), and Hoffmann and Hecht (1990) have discounted the effect of polonium-210 at its level in MS in lung-cancer causation in active smokers (see **Table 4**). The IARC (1980c) considers the evidence "limited" to support the carcinogenicity of cadmium in humans; because of the available data base, Hoffmann and Hecht (1990) found the role of cadmium in tobacco smoke carcinogenesis difficult to evaluate. From this type of evidence, it is doubtful that these five components should be included in the two "Lists of 43."

Several specific components could and should be excluded from the "Lists of 43":

- Dibenzo[*a,l*]pyrene was reported as an MS component in 1957 on the basis of data for a PAH originally thought to be dibenzo[*a,l*]pyrene but subsequently shown in 1966 to be dibenzo[*a,e*]fluoranthene (now known as dibenz[*a,e*]-aceanthrylene).
- The failure of several research groups to confirm the presence of the aza-arenes (7*H*-dibenzo[*c,g*]carbazole, dibenzo[*a,h*]acridine, and dibenz[*a,j*]acridine) in MS.
- The discontinued use in tobacco agriculture of the diethanolamine salt of maleic hydrazide, the only known precursor of *N*-nitrosodiethanolamine in tobacco and its smoke.
- *N*-Nitrosomorpholine has not been detected in MS, SS, or ETS.
- Because several of the listed components (formaldehyde, acetaldehyde, crotonaldehyde, ethyl carbamate, hydrazine) are highly water-soluble, a large proportion of their amount is scrubbed from MS by the aqueous fluids coating the surfaces of the oral cavity and trachea, thus reaching the lung at a substantially reduced level. A similar phenomenon will occur with these components in ETS.
- The only quantitative MS data for many of the listed components were obtained from pre-1970 cigarettes. In several instances, only one value has ever been reported, *e.g.*, 5-methylchrysene, DBA, dibenz[*a,h*]acridine, 7*H*-dibenzo[*c,g*]-carbazole. Thus, their presence in tobacco smoke cannot be considered confirmed.

Below are summarized some of the reasons to exclude many, if not all, of the 50 components listed by OSHA and EPA.

Component	OSHA List	EPA List[a]	Inhalation Toxicology: SCC[b] Production	Comments
Polycyclic Aromatic Hydrocarbons:	The 13 PAHs listed plus others with tumorigenic and/or promoting or cocarcinogenic activity account for less than 2% of the response observed in laboratory animals painted daily with massive doses of CSC over their life span. Except for BaP, none of the 13 PAHs is categorized by IARC as a human carcinogen. BaP is categorized as a "probable human carcinogen."			
1. benz[*a*]anthracene (BaA)	✓	✓	no	Various authorities categorize the activity of BaA from nontumorigenic to weakly tumorigenic in animals only.
2. benzo[*b*]fluoranthene {benz[*e*]acephenanthrylene}	✓	✓	no	⎧ Comparisons of MS levels of these PAHs and their ⎪ tumorigenicity in animals studies (skin painting)
3. benzo[*j*]fluoranthene		✓	no	⎨ relative to those of BaP indicate these three PAHs ⎪ contribute little to tobacco smoke tumorigenicity.
4. benzo[*k*]fluoranthene	✓	✓	no	⎩
5. benzo[*a*]pyrene (BaP)	✓	✓	yes	Lung tumor production in laboratory animals treated with massive doses of BaP via inhalation was rated "equivocal" by RTECS.
6. chrysene		✓	no	IARC characterized the evidence supposedly indicating the tumorigenicity of chrysene in animals as "limited."
7. chrysene, 5-methyl-	✓	✓	no	Instability of methylchrysenes in air precludes the long time presence of this PAH in ETS.
8. dibenz[*a,h*]anthracene (DBA)	✓	✓	no	
9. dibenzo[*a,e*]pyrene {naphtho[1,2,3,4-*def*]chrysene}	✓		no	
10. dibenzo[*a,h*]pyrene {dibenzo[*b,def*]chrysene}	✓		no	
11. dibenzo[*a,i*]pyrene {benzo[*rst*]pentaphene}	✓	✓	no	
12. dibenzo[*a,l*]pyrene {dibenzo[*def,p*]chrysene}	✓	✓	no	Is this the PAH incorrectly identified in the 1950s as dibenzo[*a,l*]pyrene but subsequently shown to be the isomeric (and nontumorigenic) PAH, dibenz[*a,e*]-aceanthrylene?
13. indeno[1,2,3-*cd*]pyrene	✓	✓	no	
Aza-Arenes:	None of the four aza-arenes listed is categorized by IARC as a human carcinogen. IARC does not even categorize quinoline as an animal carcinogen.			
14. quinoline		✓	no	
15. dibenz[*a,h*]acridine	✓	✓	no	⎧ Seven studies conducted during the period 1963 to ⎪ 1987 failed to confirm the presence of these three
16. dibenz[*a,j*]acridine	✓	✓	no	⎨ aza-arenes in cigarette MS; in no study since
17. 7*H*-dibenzo[*c,g*]carbazole	✓	✓	no	⎪ 1963 has their presence been detected. ⎩
N-Nitrosamines:	None of the NNAs listed by OSHA or EPA is categorized as a human carcinogen by the IARC.			
18. *N*-nitrosodimethylamine (NDMA)	✓	✓	yes	Lung tumor production in laboratory animals treated with massive doses of NDMA via inhalation was rated "equivocal" by RTECS.
19. *N*-nitrosoethylmethylamine (NEMA)		✓	no	

Component	OSHA List	EPA List[a]	Inhalation Toxicology: SCC[b] Production	Comments
N-Nitrosamines (cont.):				
20. *N*-nitrosodiethylamine (NDEA)	✓	✓	yes	Lung tumor production in laboratory animals treated with massive doses of NDEA via inhalation was rated "equivocal" by RTECS.
21. *N*-nitrosodipropylamine (NDPA)	✓		no	In tumorigenicity studies with members of an homologous series, the activity usually decreases as the molecular weight increases, *e.g.*, the activities of the NNAs are as follows: NDMA > NDEA >> NDPA >> NDBA. Comparison of the levels of NDPA and NDBA in MS and their activities relative to NDMA indicates that these two NNAs contribute little to the tumorigenicity observed in laboratory animals.
22. *N*-nitrosodibutylamine (NDBA)	✓		no	
23. *N*-nitrosopyrrolidine (NPYR)	✓	✓	no	
24. *N*-nitrosodiethanolamine (NDELA)	✓	✓	no	Precursor of NDELA has been banned from use in U.S. tobacco agronomy since 1981. If NDELA follows the pattern of arsenic and DDT, its levels in tobacco and smoke should have diminished accordingly.
25. *N'*-nitrosonornicotine (NNN)	✓	✓	no	Even OSHA (1994) categorizes NNN as only an "animal carcinogen."
26. 4-(*N*-methylnitrosamino)-1-(3-pyridinyl)-1-butanone (NNK)	✓	✓	no	OSHA (1994) noted that "relevant information [is] not available" on the tumorigenicity of NNK in humans.
27. *N'*-nitrosoanabasine (NAB)		✓	no	
28. *N*-nitrosomorpholine (NMOR)		✓	no	Not identified to date as a tobacco smoke component.
29. *N*-nitrosopiperidine (NPIP)	✓		no	NPIP has only occasionally been detected in cigarette MS.
Aromatic Amines:				
30. 2-toluidine {aniline, 2-methyl-}	✓	✓	no	In the 1981 and 1982 Surgeon General's reports (USPHS, 1981, 1982) it is noted that the etiological significance of these trace amines, considered individually or *in toto*, in MS is questionable. Even Hoffmann *et al.* noted that the amount of 2-naphthylamine in MS was too low to be considered a health hazard.
31. 2-naphthylamine	✓	✓	no	
32. biphenyl, 4-amino-	✓	✓	no	
Aldehydes:				
33. formaldehyde	✓	✓	no	Because of their water solubility, only a small proportion of formaldehyde, acetaldehyde, and crotonaldehyde in tobacco smoke reaches the lung. Fluids covering the oral cavity and trachea "scrub" them from orally-inhaled MS or ETS. In the case of nasally-inhaled ETS, a large proportion of each of them is removed by "resorption."
34. acetaldehyde	✓	✓	no	
35. crotonaldehyde		✓	no	

Component	OSHA List	EPA List[a]	Inhalation Toxicology: SCC[b] Production	Comments
Miscellaneous Organic Compounds:				
36. benzene	✓	✓	no	In thousands of studies with PAHs, benzene was the solvent used. Tumors at the site of painting with benzene alone (the solvent controls) were a rarity as were tumors at sites other than the painted area. Leukemia was seldom reported in any of the thousands of animals used between 1932 and the mid-1950s when acetone became the solvent of choice.
37. styrene {benzene, ethenyl-}	✓		no	
38. acrylonitrile	✓	✓	no	Hoffmann and Hecht (1990) reported that the role of acrylonitrile in tobacco carcinogenesis is difficult to evaluate because of lack of data.
39. hydrazine, 1,1-dimethyl-	✓	✓	no	
40. propane, 2-nitro-	✓	✓	no	According to Hoffmann and Hecht (1990), the organospecificity (liver) of 2-nitropropane suggests it does not play a major role in tobacco carcinogenesis.
41. vinyl chloride	✓	✓	no	
42. ethyl carbamate {urethane}	✓	✓	no	Because of its water solubility, a large proportion of ethyl carbamate will be removed by oral and tracheal secretions when MS or ETS is inhaled orally; it will be removed by "resorption" during nasal inhalation of ETS.
43. DDT {ethane, 1,1,1-trichloro-2,2-*bis*(*p*-chlorophenyl)-}	✓		no	Discontinued use of DDT in tobacco agronomy resulted in a decrease in the level of DDT in tobacco from 52 to 0.2 μg/g within a decade.
Inorganic Components:				
44. hydrazine	✓	✓	no	Because of its water solubility, a large proportion of hydrazine will be removed by oral and tracheal secretions when MS or ETS is inhaled orally; it will be partially removed by "resorption" during nasal inhalation of ETS. IARC rates the evidence "inadequate" to classify hydrazine as a human carcinogen.
45. arsenic	✓	✓	no	Discontinued use of arsenicals in tobacco agronomy resulted in a decrease in the level of arsenic in tobacco from more than 50 μg/g to about 0.5 μg/g between 1950 and 1970.
46. nickel	✓	✓	no	
47. chromium	✓	✓	no	{ According to Hoffmann and Hecht (1990), compilers of the list used by EPA, it is difficult to evaluate the roles of chromium, cadmium, and lead in tobacco carcinogenesis given the currently available data basis.
48. cadmium	✓	✓	yes	
49. lead	✓	✓	no	
50. polonium-210	?[c]	✓	yes	The significance of ^{210}Po in tobacco smoke-induced lung cancer has been questioned upon comparison of data from tobacco smokers with those obtained in miners. The Surgeon General (USPHS, 1982) considers ^{210}Po a questionable risk factor for lung cancer in active cigarette smokers.

[a] The EPA list of 43 components is that of Hoffmann and Hecht (1990). [b] SCC = squamous cell carcinoma

[c] OSHA's list of 43 contains only 42 items! It is suspected that polonium-210 is the omitted component.

Examination of data for the 35 tobacco smoke components included by OSHA and EPA as significant "tumorigens" reveals the following:

- Of the **nine** PAHs included on OSHA's and EPA's lists, only one — BaP — is classified by IARC as a "probable human carcinogen." Findings on the production of lung tumors (squamous cell carcinomas) in laboratory animals exposed to BaP by inhalation have been rated "equivocal" by the RETCS.
- Of the **three** aza-arenes included on OSHA's and EPA's lists, the presence and levels of the three in MS (and ETS) are highly questionable. In six different investigations between 1963 and 1987, none of the three has been detected in MS (or SS).
- Of the **six** NNAs common to OSHA's and EPA's lists, none has been classified as a human carcinogen. Findings on the production of lung tumors (squamous cell carcinomas) in laboratory animals exposed to NDMA or NDEA by inhalation have been rated "equivocal" by the RTECS.
- Of the **three** aromatic amines included in OSHA's and EPA's lists, none is considered a respiratory tract tumorigen. Even one of the authors of the list used by EPA considers the levels in MS of the three amines to be too low to be significant in bladder cancer.
- Of the **two** water-soluble aldehydes common to both lists, neither present in orally inhaled MS or ETS reaches the lung at the level anticipated because of "scrubbing" from the smoke stream by fluids coating the surfaces of the oral cavity and trachea. Similarly, neither in nasally inhaled ETS reaches the lung at the level anticipated because of "resorption" in the nasal cavity.
- Of the **six** miscellaneous organic components in both OSHA's and EPA's lists, one — the water-soluble ethyl carbamate — does not reach the lung at the level anticipated because it is "scrubbed" or "resorbed" during oral or nasal inhalation of ETS, respectively. Benzene is not a respiratory tract tumorigen. The levels in MS (or ETS) of the other four preclude their significant involvement in lung cancer production in active smokers.
- Of the **six** inorganic components common to both lists, one — the water-soluble hydrazine — does not reach the lung at the level anticipated because it is "scrubbed" or "resorbed" during oral or nasal inhalation of ETS, respectively. The other five components (arsenic, nickel, chromium, cadmium, and lead) are not considered significant in tobacco smoke carcinogenesis in smokers by the Surgeon General, by IARC, and by Hoffmann and Hecht, authors of the list used by EPA.

Additional and more detailed reasons for exclusion of many of the 50 components from the two "Lists of 43" are presented in Table 4. When the levels of the 50 components in MS, SS, or ETS are compared to the massive levels generally used in the various experiments with laboratory animals to define the "carcinogenicity" of the 50 components administered by routes other than inhalation, good arguments can be advanced to exclude all 50 components from the lists.

The formulation and use of lists of "tumorigenic" or "carcinogenic" materials such as the two "Lists of 43" proposed by Hoffmann and Hecht (1990) and OSHA (1994) appear to be deliberate attempts to mislead the reader. It is implied — not only in the formulation of such lists by OSHA or Hoffmann and Hecht but also in their citation by agencies such as OSHA, EPA, the Surgeon General — that the components listed are carcinogenic to smokers or nonsmokers at the levels found in MS, SS, or ETS.

- **Assertions That It Is Biologically Plausible That ETS Exposure Causes Lung Cancer in Humans Ignore Ample Evidence of a Threshold Limit Value for Most of the Tumorigens Listed**

Theoretically, tumorigens are considered by OSHA, EPA, and other governmental agencies to have a "zero" threshold limit value. However, ample evidence has been provided since the first successful production of tumors in laboratory animals by radiation in 1910 and by skin-painting with coal tar in 1915 that a practical threshold limit value does exist for known tumorigens. This has been demonstrated not only for MS CSC but also for several of the MS components on the "Lists of 43." In a lifetime mouse skin-painting experiment, a 3.3-fold dose reduction from 10 to 3 g CSC/mouse/year reduced the % tumor-bearing animals (% TBA) from 60 to 0%; in the massive NCI TWG "less hazardous" cigarette study, an 8.3-fold dose reduction from 25 to 3 mg/mouse/day reduced the percentage TBA from 46 to 1% (**Table 18**).

In dose-reduction studies with individual MS components such as BaP and dibenz[*a*,*h*]anthracene (DBA), the tumorigenicity eventually is reduced to zero at a finite dose level, *e.g.*, a 10-fold reduction in BaP administered (equal volumes of 0.005% *vs* 0.0005% solution) in a skin-painting study reduced the percentage TBA from 55 to 0% (**Table 20**); a 10-fold dose reduction from 10 to 1 μg of DBA injected subcutaneously resulted in no sarcoma-bearing animals in the 1-μg group.

Similar results were found by dose reduction of MS components or MS fractions demonstrated to be *in vitro* ciliastats: When MS CSC is divided into phenolic, acidic, neutral, basic, and "insoluble" fractions, dose reductions ranging from 6-fold to 24-fold — depending on the fraction studied — reduced the observed ciliastasis from "immediate and complete" to "zero" (**Table 21**). Studies with individual MS components (aldehydes, ketone, phenols) have produced similar results (*cf.* **Table 22**).

A substantial proportion of MS components shown to be ciliastatic in *in vitro* systems is removed during human smoking from the MS because they are extremely soluble in the fluids coating the oral cavity and laryngeal area. Less than a third of these components reach the ciliated area of the lung. Similarly, when inhaled through the nose (as in the case of ETS), water-soluble compounds such as formaldehyde, acetaldehyde, and crotonaldehyde are removed from the smoke stream by "resorption." Several of the "tumorigens" (formaldehyde, acetaldehyde, crotonaldehyde, ethyl carbamate, hydrazine) on the "Lists of 43" are highly water-soluble and are or would be removed from MS and ETS in the oral and nasal cavity, respectively. Thus, their effect on ciliated lung tissue, if any, because of their presence in inhaled MS or ETS and their subsequent contribution to lung cancer development in active and passive smokers would be much less than predicted from their MS or ETS levels.

This dilution effect has been demonstrated in numerous studies involving the exposure of nonsmokers to ETS. Exposure of nonsmokers to ETS and exposure of active smokers to MS have been studied with regard to changes in urinary mutagenicity, nicotine and cotinine levels in body fluids, and carboxyhemoglobin (COHb) formation. In the majority of the studies, increases in these parameters were slight for ETS-exposed nonsmokers, and these increases are not viewed as either statistically significant or representing any toxicological problem (**Tables 29** and **31**). These findings indicate that the ETS-exposed nonsmoker inhales significantly less of the smoke components allegedly responsible for the effect studied than does the MS-exposed active smoker.

For several MS components, comparison data are available for their levels in MS and ETS. Obviously, ETS — to which the nonsmoker is exposed — is highly dilute compared to MS. This high degree of dilution is reflected in the MS/ETS dilution ratios for nicotine (ranging from 57,000 to 7,200,000) (**Table 26**), acrolein (1,500 to 20,800), acetone (240 to 2,000), benzene (112 to 7,000), and BaP (68 to 40,000). If dose reductions of at least 25:1 nullify the tumorigenic effects of MS, MS CSC, and MS CSC components on laboratory animals or nullify the ciliastatic activity in laboratory animals of

MS CSC fractions or MS VP components, the dilutions ranging from a low of 68 for BaP to a high of 7,200,00 for nicotine suggest that it is biologically implausible for ETS exposure to elicit lung cancer.

Additionally, inhalation studies in laboratory animals exposed to high dose levels of MS have consistently failed over the past four decades to produce lung tumors in exposed animals of the tumor type statistically associated with smoking in humans. Many of these studies were conducted with the MS diluted 10:1 with air because of the animals' size. If positive results have never been obtained at a 10:1 dilution, it is obvious that further dilution — such as that encountered in ETS and noted above — would be highly unlikely to produce a positive result. OSHA attributed the failure to produce such tumors on the delivery of an insufficient dose of MS. OSHA omitted reference to much data which showed a large proportion of the tobacco smoke administered to the test animals successfully reached the target area. It also did not acknowledge that such tumors have been successfully produced via inhalation in laboratory animals treated similarly with Diesel exhaust gases.

- **ETS Contains a Number of Tumor Inhibition Agents and Anticarcinogens That Must Be Considered When Predicting Its Tumorigenic Potency**

Despite the limitations of the experimental data indicating tumorigenicity and the applicability of these data to the human situation, OSHA personnel (and EPA personnel) have accepted as valid the categorization of the components in the "Lists of 43" as "tumorigenic." It is known that MS (as well as SS and ETS) contains, in addition to the "tumorigenic" components in the "Lists of 43," a great number (> 100) of components (**Table 32**) known to be inhibitory or anticarcinogenic to many of the components in **Table 4**. Many of these inhibitors and anticarcinogens are present in MS at levels substantially greater than most of the listed "tumorigens." This ratio of anticarcinogen:tumorigen observed in MS is essentially the same in ETS since many of the anticarcinogens and inhibitors such as the phytosterols, α-tocopherol, and the saturated aliphatic hydrocarbons have molecular weights and vapor pressure properties similar to those of the listed tumorigens and thus do not evaporate from the particle.

- General Comments

Despite the fact that repeatedly throughout its notice of proposed rulemaking OSHA qualifies many of its statements with such words as "may", suggest", "probable", and the like, OSHA states its conclusion, based on numerous equivocal statements, with great certainty.

OSHA also appeared to select literature citations to mislead the reader. *E.g.*, in its discussion of the "few experimental inhalation studies with sidestream smoke or ETS reported in the literature," OSHA reviewed 14 studies, only two of which dealt with ETS. One dealt with an implanted not inhaled SS fraction. The remaining 11 reports dealt with MS inhalation studies. After a detailed discussion and obviously biased discussion of the difference in lung cancer incidence in pet dogs owned by smokers *vs* nonsmokers, OSHA tersely ends the discussion, noting the study lacked significance because of the small sample size!

Many times throughout the document, OSHA implies that chemical and/or biological findings found with MS and/or SS may be directly extrapolated to ETS. OSHA personnel should know that this is not scientifically accurate.

Fairness of public policy requires consideration of all available evidence, especially the evidence in the form of objective scientific data. Selective use of data to support conjectures that, in turn, support preconceived agenda will not lead to defensible policies, and it is certainly reprehensible science. The evidence presented here, if objectively examined by OSHA, should significantly influence its assessment of the contribution of ETS to indoor air.

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Shear and Leiter (1941): *[T]he term 'carcinogenic potency'...is not to be considered as an invariable property inherent in a compound but is merely a summary of the results of particular experiments and is valid only for animals of the species, strain, sex, age, diet, etc. of the particular animal employed as well as the dose, menstruum, mode and site of application, etc., of the compound in question... Conclusions regarding the potency of any given compounds should therefore be interpreted in the light of the data upon which they are based.*

Hartwell (1951): *Another pitfall is the attempt to carry over, without reservation, to man, conclusions based on animal experiments. We do not know whether man is more or less susceptible than mice to particular carcinogens. Some animal species, such as the rat, rabbit, and dog are much more resistant than is the mouse, and* vice versa...

THE CHEMICAL COMPOSITION OF ENVIRONMENTAL TOBACCO SMOKE: SOME COMMENTS ON THE OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION'S NOTICE ON 'INDOOR AIR QUALITY' (OSHA, 1994)

Introduction

Throughout its notice on "Indoor Air Quality," it is obvious that OSHA relies heavily on conclusions presented by EPA (1992) on the supposed hazards of ETS. *E.g.*, OSHA (OSHA, 1994) stated:

> EPA concluded that exposure to ETS presents an excess risk of induction of cancer in humans (p. 15970).

and

> [T]he EPA concluded, "recent evidence suggests that passive smoking has subtle but statistically significant effects on the respiratory health of adults." (p. 15977)

The EPA's reliance on severely criticized epidemiological data was discussed by Huber (1990), Huber *et al.* (1992), Aviado (1993), Holcomb (1993), and Gori (1994a, 1994b) with rebuttals to Gori's comment presented by Farland *et al.* (1994) and Jinot and Bayard (1994). As noted by Rodgman (1991, 1992), EPA also relied on inaccurate and/or incomplete information on the chemical and physical properties of ETS and on the biological properties of 43 of its components.

The Definition of ETS

The definition that OSHA uses for ETS is an incomplete one. OSHA (1994: at pages 15973, 15987):

> ETS is composed of exhaled mainstream and sidestream smoke... MS is generated during puff-drawing in the burning cone and hot zones; it travels through the tobacco column and is inhaled by the smoker. The smoke which is exhaled by the smoker, while different from the inhaled smoke, is also considered "mainstream." SS is formed between puff-drawing and is emitted directly from the smoldering tobacco product in ambient air.

OSHA apparently overlooked the contribution to SS of the tobacco smoke products which diffuse through the cigarette paper into the ambient air *during the puff*. The generally accepted definition of ETS is as follows:

ETS comprises *diluted* and *aged*: (**A**) exhaled MS (*i.e.*, the MS not retained by the smoker), (**B**) SS generated during the puff (including, in the case of the cigarette, vapor-phase components diffusing from the tobacco rod through the cigarette paper), and (C) SS generated during the smolder period between puffs.

Generally, on a weight basis, **C >> A > B**. Together, the two SSs, **B + C**, contribute from 85 to 90% of ETS. The exhaled MS, **A**, contributes from 10 to 15% of ETS (Huber, 1990).

In contrast to studies on ETS, an extremely dilute and usually aged system, studies on the compositions of MS and SS have traditionally involved the fractionation of fresh, *i.e.*, unaged, and undiluted smokes collected by well-defined procedures.

Some General Comments on the Composition of MS, SS, and ETS

Tobacco is considered by many to be an extremely complex plant material; some 3,000 tobacco components have been identified to date. Its complexity is probably no greater than that of many other plant materials, but the intensive study since the early 1950s of tobacco composition and of the relationship of its composition to that of its combustion products has inflated the view of the coplexity of tobacco. Of all the various consumer products studied during the past four decades, *e.g.*, beverages (milk, coffee, tea, wine, beer, liquor), meats (broiled, roasted, smoked), none has been subjected to a scrutiny as intense as that directed at tobacco and its combustion products.

The number of identified components in MS is presently about 4,800, of which about 4,100 are present in MS particulate phase (PP) and some 1,000 are present in MS vapor phase (VP). The total exceeds 4,800 because some MS components are found in both phases; *e.g.*, phenol, cresols, hydrogen cyanide. Soon after glass capillary gas chromatography became available for the fractionation and analysis of MS, it was estimated from the chromatographic evidence that the number of smoke components ranged from 4 to 20 times the number identified; *e.g.*, Wakeham (1971, 1972) noted in the early 1970s when the identified components in tobacco and tobacco smoke numbered about 1,350:

> Gas chromatographic scans indicate there are many more, probably over ten thousand, possibly even a hundred thousand.

In the two decades since Wakeham's comments, some additional 3,500 MS components have been identified. The MS VP and PP components identified to date (about 4,800) account for some 97% of the weight of the MS generated during the smoking of the cigarette. The large number of presently unidentified MS components are estimated, from various chromatograms and analytical spectra, to be present at nanogram and subnanogram levels.

The number of components identified to date in SS and ETS is about 320 (see **Appendix A**) and about 50, respectively. Because the effort to date to define the composition of SS and ETS has been limited (in comparison to the 40-year effort on MS composition), some authorities limit their discussions on SS and ETS composition and properties only to those allegedly harmful components actually identified in SS and ETS, respectively (Aviado, 1990; Huber, 1990). It should be recalled that extensive research in the nearly four decades since 1954 on the composition of cigarette MS has resulted in an almost 50-fold increase in the number of identified MS components [from fewer than 100 (Kosak, 1954) to the more than 4,800 known

today].

The Relationship Among the Compositions of MS, SS, and ETS

Although OSHA recognizes some of the differences and similarities between MS and SS, throughout its report, it repeatedly intimates that ETS is equivalent chemically to MS and/or SS. *E.g.*, OSHA (1994: at pages 15979, 15988) stated:

> [T]he corroborative evidence of the carcinogenicity of tobacco smoke provided by animal bioassays and *in vitro* studies and the chemical similarity between mainstream smoke and ETS clearly establish that ETS is also a human lung carcinogen... There are substantial similarities and some differences between MS and SS emissions from cigarettes.

Throughout its report, OSHA generally fails to take into account the effect of the high degree of dilution on the properties of ETS and the fact that ETS is a dynamic system whose composition is dependent on a host of factors (see below).

With no evidence to the contrary, there is an extremely high probability that:

a. The chemical composition of exhaled MS is qualitatively the same as but quantitatively different from that of the MS generated and inhaled from a cigarette. Since there is no evidence to indicate that any MS component is 100% absorbed and retained in the respiratory tract of a smoker, every component present in the inhaled MS will also be present in the exhaled MS.

   The distribution of components between the VP and the PP will be different in inhaled MS from that in exhaled MS. The physical difference between inhaled and exhaled MS particles will be discussed below.

b. The chemical composition of SS produced either during the puff (intrapuff SS) or during the smolder between puffs (interpuff SS) is qualitatively similar to but quantitatively different from that of MS. No component has been identified in SS that has not been identified in MS.

c. With sufficient time and effort, any compound found in MS could eventually be identified in SS. This is also true for ETS, but because of the extreme dilution of ETS, the time and effort required to identify all the ETS components corresponding to those known in MS would be tremendous.

The "100-plus" SS components noted by Aviado (1990) [*cf.* alternative statement by the IARC (1986) which noted that "...about 300-400 of the more than 3800 compounds in tobacco smoke have so far been determined quantitatively in MS and SS..."] as having been identified to date simply reflect the extent of the isolation/identification effort to date.

By 1990, more than 300 components had already been identified in SS (Klus and Kuhn,

1982; Sakuma *et al.*, 1983a, 1983b, 1984a, 1984b; R. J. Reynolds Tobacco Co., 1988; Eatough *et al.*, 1990a; Klus, 1990) (see **Appendix A**). In many of these reports, the authors emphasize the SS/MS ratio for the levels of components of interest in freshly generated, unaged and undiluted MS and SS. These ratios have been used inappropriately by some authors and institutions, including EPA and OSHA (OSHA, 1994: see Tables III-6 and III-7), to extrapolate the claimed adverse effect of MS to ETS via SS and the SS/MS ratio. Because of the nature of ETS, SS/MS ratios are not relevant to ETS.

Many authors neglected to differentiate among the substantial differences in the chemical and physical properties of freshly generated unaged and undiluted SS, of aged and diluted SS, and of ETS. Those unfamiliar with these differences have mistakenly interpreted the statements in many of these publications as proof that SS and ETS are equivalent. Huber (1990) noted with regard to the use of these SS data:

> [L]inear risk extrapolations were...calculated, not on the basis of real exposure to ETS, or on the basis of quantified or measured exposure to ETS, but rather on the basis of chemical determinations of sidestream smoke constituents. Except under the most unusual circumstances, humans are not exposed to sidestream smoke, at least, that is to sidestream smoke as it is characterized and assessed by chemists.

Part of the problem of SS component isolation and identification is the relative difficulty of collecting the requisite large quantities of SS for analysis *vs* the relative ease of collection of large quantities of MS. This difficulty is further compounded in the collection of sufficiently large quantities of ETS which, by its very nature, is not only an extremely dilute aerosol system but also a dynamic one. The extreme dilution of ETS in a given room space would necessitate the processing of extremely large volumes of air to further define ETS composition.

The dynamic nature of ETS results from several ongoing processes and/or conditions in the room space; *e.g.*, ventilation, air circulation, air exchanges per unit time, temperature, relative humidity, and the nature of surfaces exposed to ETS. Many ETS components will be adsorbed on various furniture and floor covering fabrics, wall coverings, etc. Thus, they will be removed from the room air and not be amenable to collection and analysis. This "decay" of ETS components will obviously vary from component to component and will depend on component-surface reactivity. If such parameters as air flow, temperature, and/or relative humidity were to increase after ETS-component adsorption on surfaces, some components may subsequently be desorbed from the surface into the air and thus be available again for collection and analysis [*cf.* the findings of Nelson *et al.* (1989) on nicotine in ETS].

Weiss *et al.* (1983) have commented on the difficulties encountered in determining the levels of and exposure to ETS components:

> [A]dequate characterization of passive exposure in both epidemiologic and physiologic studies is substantially more difficult (than in the case of active smoking). While the active smoker's total current cigarette consumption is relatively easily quantitated, the lower dose and greater influence of ventilation and ambient environment for the passive smoker makes [*sic*] assessment of exposure one of the most important methodologic issues.

Huber (1990) noted not only the difficulties in measuring levels of and exposure to ETS but also that there were no specified analytical methods for ETS determination such as those prescribed by the FTC for MS "tar," nicotine, water, and CO determinations and some of the methods recently used for determination of the levels of specific ETS components such as the *N*-nitrosamines (NNAs) were subject to errors because of their artifactual formation during smoke collection of the NNAs under study.

From the following premises, we can assess logically the relationship between the chemical composition and the possible biological effects of ETS in the human situation:

a. ETS comprises aged and diluted exhaled MS and intra- and interpuff-generated SS.

b. The high probability that all of the MS components, including the over 4800 identified ones, are present in exhaled MS and in intra- and interpuff-generated SS, and thus are present in ETS.

c. The high probability that the compositions of exhaled and inhaled MS, intra- and interpuff-generated SS, and ETS are qualitatively the same but quantitatively different.

d. The fact that ETS is a highly diluted mixture of exhaled MS and intra- and interpuff-generated SS.

With regard to c. above, Eatough *et al.* (1990a, 1990b) noted:

> Sidestream and mainstream smoke are qualitatively similar. However, significant quantitative differences exist between the two sources.

In addition to the profound quantitative differences among the chemical compositions of MS, SS, and ETS, there are major differences in their physical properties which influence the degree of ETS exposure experienced by the nonsmoker.

Despite OSHA's attempt to convince the reader that it understands the substantial physical and chemical differences among MS, SS, ad ETS, it repeatedly implies throughout the report that ETS is equivalent to MS or SS (see OSHA, 1994: at 15979, 15980, 15982).

The Physical Properties of MS, SS, and ETS

An aerosol is defined as a colloidal system of dispersed liquid or solid material in a gaseous medium: Cigarette smoke is an aerosol comprising liquid droplets in a gas.

For nearly two decades, investigators have accumulated knowledge on the conditions involved in the formation of MS and SS aerosols during the smoking of a cigarette and the factors contributing to or modifying their yields and composition. Theories on smoke formation in vogue in the late 1950s and early 1960s were demonstrated to be incorrect; *e.g.*, many investigators thought that all smoke components not originally present in tobacco and thus

appearing in the MS by pyrogenesis from the tobacco were formed at or near the fire cone at temperatures in excess of 900 °C. New and more nearly correct theories replaced the old ones. Advances in our knowledge of smoke formation and transport were possible because of improved technologies developed to accomplish the following tasks (*cf.* Townsend, 1987):

- Accurately measure temperatures during puffs and during the smolder period between puffs at various sites within the burning cigarette and its fire cone.

- Follow the formation of specific components and their subsequent passage and transport, in the case of MS components, through the tobacco rod by puff-driven volatilization, repetitive condensations and revolatilizations, filtration by tobacco rod and filter tip material, etc.

- Follow the formation of specific components and their subsequent emission, in the case of SS components, to the atmosphere.

Baker (1976, 1979) has written at length on his original research and that of others on MS and SS aerosols and the conditions involved in the cigarette in their formation and transport. He has also periodically authored several excellent and detailed reviews (1980, 1984, 1987a, 1987b, 1990) on this subject.

It is now known that the fire cone temperature of 900+°C measured during the puff primarily generates gaseous components such as the carbon oxides, water, ammonia, nitric oxide, etc. During the puff, pyrogenesis of most MS components occurs in a 3- to 4-mm cylinder of the tobacco rod a few millimeters behind the fire cone:tobacco rod interface where the temperature ranges from 500 to 650°C. During the smolder period, the fire cone temperature is 500 to 600°C, and it is at this temperature that SS is generated from the tobacco.

Just as profound quantitative differences exist among the chemical compositions of fresh and aged MS, fresh and aged SS, and ETS, there are several differences in the physical properties of these smokes. One physical property important in these various types of cigarette smoke, their inhalation, and their retention is their particle size. There are several ways to describe particle size. A frequently used one is mean mass aerodynamic diameter (MMAD).

In his review of the aerosol studies on cigarette smoke, Ingebrethsen (1986a) points out that two factors are extremely important with respect to the measured particle size of an aerosol:

- The time between aerosol generation and particle size measurement.

- Concentration of the aerosol.

High aerosol concentration and extended time between generation and measurement result in increased coagulation of particles and increased particle size. Freshly generated MS and SS have the major fraction of particle sizes, expressed as MMAD, in the range 0.3 to 0.4 μm

(Ingebrethsen, 1989). Since SS — both intra- and interpuff generated — is the major contributor, estimated at 85% to 90%, to ETS, it is important to realize that its physical properties are constantly and progressively changing. These changes begin the moment it is generated and continue during its extensive dilution as it disperses through the room until it is eventually perceived as ETS. Depending on the proximity of the measuring device to the source of the SS, it is obvious that a range of particle sizes could be found, ranging from that measured in freshly generated SS to that found in essentially equilibrated ETS. The behavior of particles in SS under carefully controlled conditions has been studied in detail by Ingebrethsen and Sears (1989).

Another problem of determining the contribution of ETS to a given air space (home, office, restaurant, aircraft, etc.) is that other non-ETS contributors to VP and PP are measured at the same time as the contribution of ETS to VP and PP is measured. These include contributions from cooking oils and foods in homes and restaurants, cleaning preparations and furniture polishes, personal products (perfumes, after-shave lotions, hair sprays, deodorants, etc.), and vehicular exhausts where the air space is adjacent to much travelled roads. Chromatographic scans of samples collected in a conference room before and after a 2-hour meeting during which smoking was permitted revealed that chromatographic peaks, some representing compounds from non-tobacco sources, were much larger than those known to be due to ETS (Green, 1980). Similar findings were reported by Bayer and Black (1987) who compared volatile organic contaminants (VOCs) in the offices of smokers and nonsmokers. The authors noted "Building materials and furnishings are the most common source of these VOCs. [The] VOC building background makes it difficult to distinguish ETS contamination from the VOCs outgassing from other sources."

A major distinction between MS and SS that affects particle composition is that MS is acidic, with a pH ranging from 6.0 to 6.6; whereas, the pH of SS ranges from 6.7 to 7.5. The SS from most cigarettes is alkaline with pH above 7.0. Under acidic conditions (pH < 7.0), smoke amines such as nicotine are protonated and have a relatively low volatility; under alkaline conditions (pH > 7.0), such amines are nonprotonated, *i.e.*, "free," and are relatively more volatile.

The differences and similarities in the physical properties among MS, SS, and ETS are summarized in **Table 1.**

TABLE 1: PHYSICAL PROPERTIES OF MS, SS, AND ETS AND EFFECT ON SMOKE PROPERTIES

Property	MS[a]	SS[a]	ETS
Number of identified components	4100 in particulate phase (PP); 1000 in vapor phase (VP). Some components are present in both the PP and VP; *e.g.*, HCN, simple phenols, volatile NNAs.	Composition assumed to be qualitatively similar to that of MS; *i.e.*, the number and identity of the SS and ETS components are the same as those in MS. Quantitative differences in component levels are substantial. The distribution of a component between PP and VP depends on the nature (acid, base, neutral) and the physical properties (vapor pressure, etc.) of the particular component. The decay (decrease) of an individual ETS component is also dependent on numerous factors such as its nature, its physical properties, and the temperature, relative humidity (RH), ventilation, and nature of surfaces (carpets, drapes, upholstered furnishings, etc.) in the smoke space.	
Approximate temperature of			
• fire cone	850-950°C	500-600°C	
• smoke formation	500-650°C	500-600°C	
Approximate weight of tobacco rod consumed[b]	30-40%	50-60%	
Particle size, μm	Fresh whole MS particles have MMAD = 0.3-0.4 μm[c] contain volatile components which readily vaporize from the particles. Because of coagulation, hydration, evaporative transfer and other physical processes, *e.g.*, the cloud effect, MS particles behave as though they have a MMAD in the micron range[c].	Fresh SS particles are about the same size as MS particles; within a short time (<100 min) after generation, the MMAD ≈ 0.2 μm[c] for SS particles.	During dilution to ETS, exhaled MS particles lose H_2O and other volatile PP components; particle size decreases to a MMAD = 0.15-0.20 μm[c]. SS particles lose H_2O and other volatile PP components such as nicotine, amines, etc. Thus, particle size decreases to a MMAD = 0.15-0.20 μm[c].
Particle concentration, #/cm^3	10^9 to 10^{10}		~1-5 x 10^5
Retention of particulate matter in respiratory tract	50 to 90% Percentage retention as measured by weight loss between time of inhalation and exhalation due to mechanical trapping plus loss of volatiles from inhaled particles.		10-11% *vs* 17-41%[d] Low percentage retention as measured by weight loss is due to virtual absence of coagulation and other physical phenomenon, *e.g.*, cloud effects, and lack of water and other volatile components which may be lost by inhaled ETS particles.
Smoke pH	6.0 to 6.6 for cigarette MS.	6.7 to 7.5 for cigarette SS. Some investigators have reported SS pH values as high as 8.0	Neutral (pH 7.0) to slightly alkaline.

Table 1: Continued

Property	MS[a]	SS[a]	ETS
Inhalability of smoke into lungs	MS inhalability favored by pH less than 7.0.	Inhalability of smoke (whether cigarette SS, pipe MS, or cigar MS) is progressively diminished as smoke pH increases above pH 7.0.	Because of extreme dilution by air and near neutrality (pH close to 7.0), the inhalability of ETS is nearly the same as that of air.
Nicotine behavior	99+% of nicotine in cigarette MS is in the PP; because the MS pH is much less than 7.0, amines such as nicotine are protonated; nicotine in MS PP is presumed to be protonated by the low molecular weight acids present in MS[e]	Because of alkalinity of SS and the high concentration of SS particles near the burning cone, nicotine (and other volatile smoke components) are distributed between the SS PP and SS VP; PP-VP equilibrium for these compounds is not attained adjacent to the cigarette burning cone.	Because of the extremely high dilution of ETS and its pH at or slightly above 7.0, little nicotine (and other amines) are found in ETS PP; more than 95% of the nicotine in ETS is in the non-protonated form and is found in ETS VP.
Relationship of smoke yield to cigarette design	MS controllable by • tobacco rod length and circumference • filter type and dimensions • filter-tip additives • tobacco blend and weight • processed tobacco (reconstitution, expansion) • paper and paper additives • air dilution (paper porosity and filter perforation)	Interpuff SS, the major contributor to total SS, is primarily controlled by cigarette tobacco blend and weight and to a lesser degree by paper properties and additives.	Since ETS comprises 85-90% diluted and aged SS plus 10-15% exhaled MS, the control of ETS resides primarily with those factors which control intrapuff SS generation.

[a] Properties listed are those for *unaged* and *undiluted* smoke.
[b] Tobacco rod not consumed during smoking estimated at 5 to 8% for filtered cigarettes; 20 to 25% for nonfiltered cigarettes.
[c] MMAD value listed is that for a major fraction of the smoke.
[d] *Cf.* % retention determinations in studies with experimentally produced ETS (Hiller *et al.*, 1982b; McAughey *et al.*, 1994).
[e] Protonation of nicotine in tobacco due to long-chained acids (palmitic acid, stearic acid, etc.) and polycarboxylic acids (oxalic acid, malic acid, citric acid).

When freshly generated MS is inhaled during smoking, the aerosol particles in the smoke are exposed in the respiratory tract to an atmosphere whose temperature is 37°C and whose relative humidity exceeds 95%. As a result, the inhaled particles absorb water and increase in size. Those particles that are exhaled are, on average, 20 to 25% larger than the inhaled particles (Ingebrethsen, 1986b, 1989; Ingebrethsen and Sears, 1989; Ingebrethsen *et al.*, 1988, 1990; Benner *et al.* 1989). When these water-saturated exhaled MS particles (temperature at 37°C) are released into the atmosphere (temperature generally below 30°C and relative humidity below 50%), they cool, and immediately undergo several evaporative processes which are completed in a few milliseconds. These processes include the following:

- Components, usually gaseous under ambient conditions, evaporate from the particle.
- Components with modest vapor pressures evaporate from the particle.

- Water, incorporated into the particle either during the smoke formation process in the tobacco rod or during its residence time in the highly humid confines of the respiratory tract, evaporates.

SS particles behave much differently than MS particles. Although little research has been conducted on fresh, undiluted SS, it is reasonable to expect that the particles are physically similar to those in MS. However, the high dilution which occurs almost immediately upon generation has the effect of preventing coagulation and promoting evaporative losses. Also, because of the alkalinity of SS, basic components are nonprotonated and readily evaporate from the particle. Studies on SS and ETS, both generally alkaline (pH > 7.0), indicate that little (< 5%) of the nicotine remains in the ETS particle, the bulk of it (> 95%) evaporates from the particle and appears in the VP (Eudy *et al.*, 1985).

As a result of these various processes, the SS and exhaled MS particles, on their way to contribute to ETS, decrease both in particle mass and in particle size to an MMAD ranging from 0.15 to 0.20 μm for the major fraction of the particles. Experimental data for the decrease in SS particles size were presented by Ingebrethsen and Sears (1989). Ten minutes after smoke generation, a major fraction of the SS particles showed a particle size with an average MMAD of 0.20 μm.

It should be noted that these various evaporative processes involve relatively volatile smoke components. The particle size is not diminished to any appreciable degree by evaporation of nonvolatile and high molecular weight components such as the PAHs {benzo[*a*]pyrene (BaP), dibenz[*a,h*]anthracene (DBA), indeno[1,2,3-*cd*]pyrene, dibenz[*a,l*]pyrene} listed by Hoffmann and Hecht (1990) and other components such as solanesol, the phytosterols, α-tocopherol, and the saturated aliphatic hydrocarbons. These components remain in the particles.

In addition to the dilution that occurs when the ETS particles disperse through the room space, an additional dilution occurs by the deposition of ETS particles on the surfaces present. These processes — evaporation, dispersion, deposition — decrease the concentration of ETS particles. Ventilation, air exchanges per unit time, nature of the surfaces (fabric, plastic, wood, etc.), temperature, relative humidity, number of cigarettes smoked per unit time, and number of persons present are some of the known variables that will also influence the concentration of ETS particles.

Questions are frequently raised about the particle size of MS, SS, and ETS and the relationship between particle size and retention in the respiratory tract of the inhaled smoke. Usually, particle size plays an important role in determining MS particulate retention in the lungs. Based on a comparison of particle size, one might expect ETS and MS to be retained similarly in human lungs on a percentage basis. Empirical data demonstrate that this is not the case. In the case of MS, other factors come into play. These drastically alter the amount of MS particulate matter that is retained. Weight-loss measurements give values ranging from 50% to 90% for the percentage retention of inhaled MS (Ingebrethsen, 1989). The percentage retention is a characteristic of the individual smoker. The retention of inhaled MS is much higher than

would be predicted by the measured MMAD of fresh smoke, 0.3-0.4 μm. Ingebrethsen (1989) has reviewed the literature on the retention of MS and identified five factors which might be responsible for increased MS particle retention. These include coagulation, electrical charge, growth by water condensation, evaporative transfer, and cloud effects. Evaporative transfer and cloud effects were deemed to be the most significant factors.

ETS particles behave quite differently from MS particles in terms of human retention. Unlike MS, the retention of ETS in the lung is not affected by evaporative transfer and cloud effects. Instead, ETS retention is mainly influenced by particle size. Theoretical calculations indicate that the percentage retention of particles equivalent in size to ETS particles should vary between 10 and 20%. A value within the theoretical range was obtained: Hiller *et al.*, from studies with human mouth-breathing volunteer nonsmokers who inhaled orally polystyrene latex spheres of particle sizes similar to those of diluted SS (Hiller *et al.*, 1982a) and with five volunteers who inhaled a tobacco smoke defined as "sidestream smoke at a concentration similar to that encountered indoors with smokers present" (Hiller *et al.*, 1982b), estimated the percentage retention of the smoke to be 11%. In a more recent study, McAughey *et al.* (1994) determined the % particulate retention in males exposed to concentrations of *aged and diluted cigarette SS* and females exposed to the higher concentration only. Particulate retentions were determined by UV measurements and by determination of % solanesol retained. For the males, the findings were consistent between the two analytical procedures; they retained 36% and 41% at the low and high concentrations, respectively. For the females, the particulate retention was much lower than for the males: 17% by the UV measurement, 27% by the solanesol method. McAughery *et al.* attributed the difference between their results, ranging from 17 to 41%, and those of Hiller *et al.* (11%) to the following:

> [T]he deposition fractions reported by Hiller *et al.* were for 0.41 μm mass median aerodynamic diameter (MMAD) smoke particles rather than the 0.14 μm MMAD particles reported in this study.

The difference in particle retention between MS and ETS is due largely to the high dilution which SS particles experience almost upon formation. This dilution causes ETS particles to behave as model, nonvolatile, inert particles by preventing coagulation, obviating cloud effects, and promoting evaporation prior to inhalation.

As noted earlier (**Table 1**), numerous technologies introduced sequentially from the mid-1950s to the late 1960s were incorporated into cigarette design to control MS delivery and composition. All are considered to contribute to what some have characterized as a "less hazardous" cigarette when included in cigarette design (USPHS, 1979; NCI, 1980; Gori and Bock, 1980; USPHS, 1981). These technologies include:

- tobacco blend and weight
- tobacco rod length and circumference
- filter tips (material type and additives)
- processed tobaccos (reconstituted tobacco sheet, expanded tobacco)
- paper (type and additives)

- air dilution (increased paper porosity, filter tip perforations).

The chronology of introduction of these technologies is noted in **Figure 1.** Over the years, use of these technologies in concert and to various degrees in cigarette design has provided the consumer with a great variety of products whose number has increased from about a dozen in the mid-1950s to nearly 200 presently. It should be remembered that the cigarette is a system: All of these technologies used in cigarette design are interactive. *I.e.*, inclusion of or change in the level of use of any particular technology may require other adjustments in the cigarette design to maintain certain attributes acceptable to the consumer. In contrast, by current technology, SS delivery is controlled almost totally by tobacco blend and weight. The SS is not subjected to filtration, the effect of filter-tip additives which specifically remove certain MS components from MS (phenols, volatile *N*-nitrosamines), or air dilution effects.

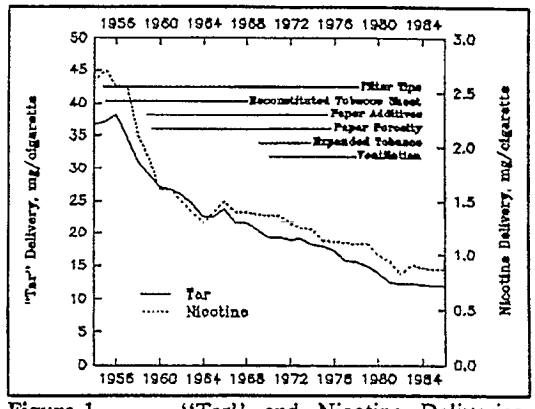


Figure 1. "Tar" and Nicotine Deliveries, Sales Weighted Average Basis

OSHA (OSHA, 1994: at p. 15988) stated:

> SS emissions, quantitatively, show little variability as a function of a number of variables [puff volume, filter versus nonfilter cigarette, and filter ventilation...]. The lack of substantial variability in SS emissions is related to the fact that they are primarily related to the weight of the tobacco and paper consumed during the smoldering period, with little influence exerted by cigarette design...

It is obvious that OSHA fails to recognize that the cigarette is a complex system in which a variety of design factors interact to influence both MS and SS emissions, *e.g.*, increasing the cigarette paper porosity will increase SS due to the emission by diffusion of various vapor-phase components *during the puff*. OSHA also cited studies (Adams *et al.*, 1987; Chortyk and Schlotzhauer, 1989) in which the data presented fail to support OSHA's view that SS emissions are "little influenced by cigarette design." The study by Adams *et al.* (1987) demonstrates that a specific combination of design factors does influence both MS and SS emissions. The data presented by Chortyk and Schlotzhauer (1989), another source cited by OSHA, not only are at odds with those from Adams *et al.* (1987) and R.J. Reynolds (1988) but also have been criticized by Green (1990).

Adams *et al.* (1987) reported data on MS and SS deliveries of 14 components in the smokes from four U. S. commercial cigarettes of different design: A nonfilter cigarette, two filtered cigarettes, and a perforated filter cigarette. In **Table 2** are summarized MS and SS delivery data for the following: TPM, nicotine, a PAH (BaP), a phenol (catechol), a volatile *N*-nitrosamine (NDMA), and a tobacco-specific *N*-nitrosamine (NNN) .

The SS TPM deliveries shown in **Table 2** for the nonfiltered and two filter-tipped cigarettes are, on average, about 50% higher than the SS TPM delivery from the perforated-filter cigarette [14.1 vs 22.3 mg/cigt {(22.6 + 24.4 + 20.0)/3) = 22.3}]. Most perforated-filter cigarettes, such as PF-D in **Table 2**, not only incorporate a perforated filter with a high percentage air dilution to reduce MS TPM but also incorporate substantial levels (30 to 50%) of expanded tobacco *in the cigarette design*. The inclusion of such a large percentage of expanded tobacco in the blend substantially reduces the weight of tobacco in the tobacco rod and the weight of tobacco consumed during the SS-generating smolder periods. Thus, these data show the SS TPM delivery from the perforated-filter cigarette is substantially less than the average of the SS TPM from the other three cigarettes. It is surprising that OSHA failed to recognize the relationship between low SS emission and cigarette design.

TABLE 2: MS/SS DISTRIBUTION OF SELECTED COMPONENTS DELIVERED BY FOUR U. S. COMMERCIAL CIGARETTES

Smoke Component, Delivery /cigt	Nonfiltered A		Filtered B		Filtered C		Perforated Filter D	
	MS	SS	MS	SS	MS	SS	MS	SS
TPM[a], mg	20.1	22.6	15.6	24.4	6.8	20.0	0.9	14.1
nicotine, mg	2.04	4.62	1.50	4.14	0.81	3.54	0.15	3.16
catechol, μg	41.9	58.2	71.2	89.9	26.9	69.5	9.1	117
BaP, ng	26.2	67.0	17.8	45.7	12.2	51.7	2.2	44.8
NDMA, ng	31.1	735	4.3	597	12.1	611	4.1	685
NNN, ng	1007	857	88	307	273	185	66.3	338

[a] TPM = total particulate matter; BaP = benzo[*a*]pyrene; NDMA = *N*-nitrosodimethylamine; NNN = *N'*-nitrosonornicotine

. In the OSHA-cited study on MS and SS deliveries from low-"tar" cigarettes, Chortyk and Schlotzhauer (1989) provided data which differ substantially from the Adams *et al.* (1987) data in **Table 2** and from other data (R. J. Reynolds, 1988) reported for comparable "tar"-delivery cigarettes. The differences in the data for comparable-"tar" delivery cigarettes were found for cigarettes delivering approximately 20, 10, and 7 mg. In their MS and SS collection and analysis, Chortyk and Schlotzhauer (1989) used their previously reported SS collection procedure (Chortyk and Schlotzhauer, 1986) in the generation of their data. Green (1990) commented on several deficiencies in the procedures used and interpretations made by Chortyk and Schlotzhauer (1989) from their data. Examination of their data and comparison of them with the Adams *et al.* (1987) and R. J. Reynolds (1988) data (see **Table 3**) reveal an additional problem: For the three cigarette categories (23-, 10-, and 7-mg "tar" deliveries), the SS/MS ratios for the TPMs in the Chortyk-Schlotzhauer study were between 2 and 7 times greater than those reported in either of the other studies from the American Health Foundation (Adams *et al.*, 1987) and R. J. Reynolds (1988). Similarly for nicotine, the Chortyk-Schlotzhauer SS/MS ratios were from about 1.5 to over 7 times greater than those reported in the other studies. These TPM and nicotine data strongly suggest a problem with their SS collection procedure.

TABLE 3: COMPARISON OF SS/MS RATIOS FOR DIFFERENT CIGARETTE TYPES

	Adams *et al.* (1987) 20-mg Cigarette			Chortyk and Schlotzhauer 23-mg Cigarette (1989)			Chortyk and Schlotzhauer 23-mg Cigarette (1986)		
Analyte[a]	MS	SS	SS/MS	MS	SS	SS/MS	MS	SS	SS/MS
TPM	20.1	22.6	1.12	21.8	56	2.57	22.9	54.9	2.40
Nicotine	2.04	4.62	2.26	1.68	9.08	5.40	1.30	5.29	4.07

	R.J. Reynolds (1988) 1R4F			Chortyk and Schlotzhauer (1989) 10-mg Cigarette			10-mg Cigarette		
Analyte[a]	MS	SS	SS/MS	MS	SS	SS/MS	MS	SS	SS/MS
TPM	11.5	16.9	1.47	10.4	60	5.77	9.5	53	5.58
Nicotine	0.79	5.60	7.09	0.90	9.10	10.11	1.05	10.46	9.96

	Adams *et al.* (1987)				Chortyk and Schlotzhauer (1989)							
	7-mg Cigarette			7-mg Cigarette			6-mg Cigarette			6-mg Cigarette		
Analyte[a]	MS	SS	SS/MS	MS	SS	SS/MS	MS	SS	SS/MS	MS	SS	SS/MS
TPM	6.8	20.0	2.94	6.7	59	8.81	5.4	60	11.11	6.0	50	8.33
Nicotine	0.81	3.54	4.37	0.58	8.95	15.43	0.22	7.04	32.00	0.55	8.06	20.77

[a] mg/cigt

The Designation by the Environmental Protection Agency of ETS as a Group A Carcinogen

After a preliminary proposal (EPA, 1990b), the U. S. Environmental Protection Agency (EPA) defined ETS as a carcinogen and categorized it as a "Group A Carcinogen" (EPA, 1992). Data from various epidemiological studies on the incidence of lung cancer in nonsmokers exposed to ETS were interpreted by the EPA as indicating that ETS was causally related to lung cancer in the ETS-exposed nonsmokers. In its report, OSHA (OSHA, 1994) essentially accepted the conclusions of the EPA on ETS.

In addition to these epidemiological data, EPA relied on data from studies on tobacco smoke composition, particularly the many studies dealing with the composition of MS as well as the smaller number of studies dealing with SS composition. Of the limited number of SS components for which quantitative data have been obtained on per cigarette deliveries, a number are delivered at higher per cigarette levels in SS than in MS. Many of the SS components quantified are those that had been considered as contributors to respiratory tract or other disease problems based upon results reported from animal experiments. EPA extrapolated these SS (and MS) qualitative and quantitative composition data directly to ETS with little regard for the profound quantitative differences between MS and SS composition and the highly diluted ETS system and the biological implications of these differences. Of prime concern to EPA were those MS and SS components which, in one biological system or other, had been previously described as tumorigenic at doses far in excess of those encountered in MS or SS (EPA, 1990b). The MS components of greatest concern to the EPA were 43 MS and tobacco components appearing in a frequently cited list, originally compiled by Hoffmann and Hecht (1990) from data presented in two IARC (1985, 1986) monographs. EPA (1990b) incorrectly assessed the health consequences with regard to lung cancer of the components in the list in the following terms:

> Of the 99 compounds in tobacco smoke that have been studied in detail, at least 43 are complete carcinogens[b], each able on its own to cause the development of cancer in humans or animals.

The EPA erred in its assessment of the 43 components in the list since most have not been shown to be (1) tumorigenic to any human tissue or (2) tumorigenic to lung tissue in laboratory animals (see summary in **Table 9**). Both of these facts are addressed in the Hoffmann and Hecht (1990) text accompanying their "List of 43." In addition, the few that have produced tumors in laboratory animals have done so at dose levels far in excess of that encountered in MS, SS, or ETS.

This year, OSHA issued its report on indoor air quality (OSHA, 1994), and the report deals at some length with ETS. OSHA presented a list of 43 tobacco smoke components for which it claims "there is 'sufficient evidence' of carcinogenicity in humans or animals." Despite the use in many places in the OSHA report of such terms as "may", "suggest", "probable", and the like when discussing the chemical composition of ETS, with particular reference to the OSHA-generated list of 43 ETS components defined by OSHA as "carcinogenic," OSHA indicts ETS in the following terms:

> OSHA's estimate of the attributable risks suggest [*sic*] that all borderline cases of lung cancer and coronary heart diseases will be prevented due to elimination of exposure of nonsmokers to ETS in the workplace.

Some examples of OSHA's use of less than definitive statements [numbers in parentheses refer to page number in OSHA (1994)] include the following:

> These parameters and others **may** result in differences in susceptibility among exposed subpopulations. (15974)
>
> These interactions **may** lead to longer retention of toxic constituents, thus prolonging the effects on the target organs resulting in tissue injury. (15974)
>
> Therefore, findings in studies conducted with respect to ETS and children **may** not be directly applicable to adults. (15975)
>
> The results of epidemiological studies taken in the aggregate **suggest** that nonsmoker exposure to ETS is causally related to the development of lung cancer. (15979)
>
> Limited existing data **suggest** that sidestream smoke **may** contain more carcinogenic activity per milligram of cigarette smoke concentrate than does mainstream smoke. (15980)
>
> These anatomical and physiological differences, aside from the subchronic exposure, **may** partially account for absence of any lung tumors in the study by Coggins *et al.* [*sic*] (15981)
>
> The epidemiological and clinical studies, taken in aggregate, indicate that exposure to environmental tobacco smoke **may** produce mucous membrane irritation, pulmonary,

[b] The citation referred to the Surgeon General's 1989 report which, in turn, reproduced the table eventually presented in Hoffmann and Hecht (1990).

cardiovascular, reproductive, and carcinogenic effects in nonsmokers. (15982)

Exposure to ETS may aggravate existing pulmonary or cardiovascular disease in nonsmokers. (15982)

In other parts of its memorandum, OSHA described 10 of its listed 43 tobacco smoke "carcinogens" as follows:

formaldehyde	**probable** human carcinogen (15987)
N-nitrosodimethylamine (NDMA)	**probable** human carcinogen (15987)
N-nitrosodiethylamine (NDEA)	**probable** human carcinogen (15987)
N-nitrosopyrrolidine (NPYR)	**probable** human carcinogen (15987)
2-toluidine	listed only as an irritant, not as a carcinogen (15987)
benz[*a*]anthracene (BaA)	**listed only** as an animal carcinogen (15987)
N'-nitrosonornicotine (NNN)	**listed only** as an animal carcinogen (15987)
4-(*N*-methylnitrosamino)-1-(3-pyridinyl)-1-butanone (NNK)	**no relevant information available** re health effects (15988)
N-nitrosodiethanolamine (NDELA)	**probable** human carcinogen (15988)
cadmium	**probable** human carcinogen (15988)

Despite these and other similar equivocal statements throughout the memorandum, OSHA states with great certainty that

> [T]he corroborative evidence of the carcinogenic activity of tobacco smoke provided by animal bioassays and *in vitro* studies and the chemical similarity between mainstream smoke and ETS clearly establish the plausibility that ETS is...a human lung carcinogen... (15979)

OSHA'S 1994 "List of 43" and Hoffmann-Hecht's 1990 "List of 43"

The Hoffmann-Hecht "List of 43" (1990) catalogs the tobacco and/or tobacco smoke components classified as "tumorigenic agents" and the per cigarette MS and SS deliveries of each; the OSHA "List of 43" simply lists 43 tobacco smoke components for which OSHA claims "there is 'sufficient evidence' of carcinogenicity in humans or animals." For the sake of discussion, the two "Lists of 43" are combined in **Table 4.**

Careful examination of this combined list reveals significant flaws in relying on it for the conclusions reached by either OSHA and EPA. Classifying a substance as "tumorigenic" or "carcinogenic" can be misleading. These terms should not be overinterpreted. Users of tables such as those promulgated by Hoffmann and Hecht (1990), EPA (1992), and OSHA (1994) must be aware of the meaning and limitations of such terms as "tumorigenicity" and "carcinogenicity" when applied to specific compounds and exercise considerable care in their use.

TABLE 4: TOBACCO AND TOBACCO SMOKE COMPONENTS LISTED AS TUMORIGENIC BY HOFFMANN AND HECHT (1990) AND TOBACCO SMOKE COMPONENTS LISTED AS CARCINOGENIC (HUMANS OR ANIMALS) BY OSHA (1994)[a]

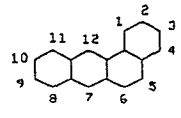
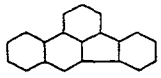
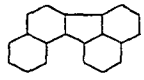
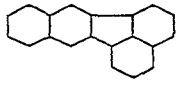
Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
			POLYCYCLIC AROMATIC HYDROCARBONS			
benz[*a*]anthracene (BaA) 	✓ [20-70 *ng*]	✓	✓		no	• Dipple *et al.* (1984) listed the tumorigenicity of BaA in animals and humans as "disputed." • Listed by OSHA (1994)[d] only as an "animal carcinogen."
benzo[*b*]fluoranthene {benz[*e*]acephenanthrylene} 	✓ [4-22 ng]	✓	✓		no	• In comparative tumorigenicity studies, the potencies of these benzofluoranthenes were reported to be much less than that of BaP: Their potencies relative to BaP were 11, 3, and 3% for benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, and benzo[*k*]-fluoranthene, respectively (Deutsch-Wenzel *et al.*, 1983). The significance of the tumorigenicity of these three PAHs is substantially diminished when their relative potencies and MS levels *vs* BaP are considered.
benzo[*j*]fluoranthene 	✓ [6-21 ng]		✓		no	
benzo[*k*]fluoranthene 	✓ [6-12 ng]	✓	✓		no	
benzo[*a*]pyrene (BaP)	✓ [20-40 ng]	✓	✓		yes	• IARC lists BaP as a "probable human carcinogen" (*cf.* Hoffmann and Hecht, 1990). • Lung tumor production with massive doses of BaP via inhalation rated "equivocal" by RTECS (1987).

Table 4: Continued

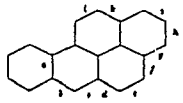
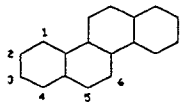
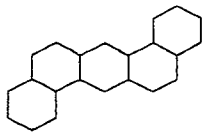
Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
			POLYCYCLIC AROMATIC HYDROCARBONS			
benzo[*a*]pyrene (BaP) *(cont.)* 	✓ [20-40 ng]	✓	✓		yes	• Listed by OSHA (1994)[d] as a "probable human carcinogen." • The range reported for MS delivery of BaP is unrealistic for current cigarettes. None of the cigarettes recently analyzed approached an MS delivery of 40 ng/cigt. The high value was 20 ng/cigt (Adams *et al.*, 1987).
chrysene 	✓ [40-60 ng]		✓		no	• Dipple *et al.* (1984) listed the tumorigenicity of chrysene in animals as "disputed." • IARC (1986) characterized the degree of evidence for the tumorigenicity of chrysene in animals or man as "limited."
chrysene, 5-methyl-	✓ [0.6 ng]	✓	✓		no	• A single value (Hecht *et al.*, 1974) for this PAH in MS based on a cigarette possibly manufactured in 1972-1973 will not be representative of its level in the MS of current cigarettes. • Because of the instability of 4- and 5-methylchrysenes (Hecht *et al.*, 1974), 5-methylchrysene may dissipate rapidly in ETS.
dibenz[*a*,*h*]anthracene (DBA) 	✓ [4 ng]	✓	✓		no	• The value for MS delivery of this PAH is presumably based on one determination, that of Wynder and Hoffmann (1963b) for a cigarette manufactured in 1962 or 1963. More recent cigarettes differ substantially in design and smoke component deliveries than those marketed three decades ago!

Table 4: Continued

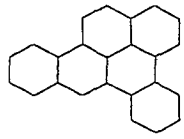
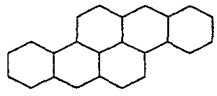
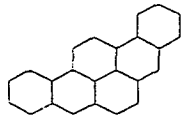
Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
***POLYCYCLIC AROMATIC HYDROCARBONS** (continued)*						
dibenzo[*a*,*e*]pyrene {naphtho[1,2,3,4-*def*]chrysene} 		✓	✓		no	
dibenzo[*a*,*h*]pyrene {dibenzo[*b*,*def*]chrysene} 		✓	✓		no	
dibenzo[*a*,*i*]pyrene {benzo[*rst*]pentaphene} 	✓ [1.7-3.2 ng]	✓	✓		no	
dibenzo[*a*,*l*]pyrene {dibenzo[*def*,*p*]chrysene}	✓ [present]	✓		✓	no	• Structure of the tobacco smoke PAH first reported as dibenzo[*a*,*l*]pyrene by Lyons and Johnston (1957), Wynder and Wright (1957), and others was subsequently demonstrated to be incorrect (Lavit-Lamy and Buu-Hoï, 1966). The PAH was actually dibenz[*a*,*e*]-aceanthrylene (originally known as dibenzo[*a*,*e*]fluoranthene), a PAH isomeric with dibenzo[*a*,*l*]pyrene.

Table 4: Continued

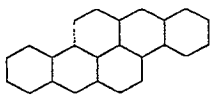
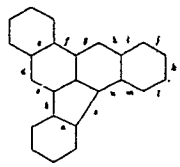
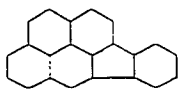
Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS Accepted	Presence in MS Controversial	Inhalation Toxicology: SCC[c] Production	Comments
POLYCYCLIC AROMATIC HYDROCARBONS *(continued)*						
dibenzo[*a,l*]pyrene {dibenzo[*def,p*]chrysene} *(cont.)*	✓ [present]	✓		✓	no	• This correction was noted and accepted by most tobacco smoke investigators, including Hoffmann and Wynder (1968). • IARC (1986) characterized the degree of evidence for the tumorigenicity of dibenz[*a,e*]aceanthrylene in animals or man as "limited." • The bonafide dibenzo[*a,l*]pyrene (dibenzo[*def,p*]chrysene) was identified in tobacco smoke by Snook *et al.* (1977) but no quantitative date were given. • Most references to dibenzo[*a,l*]pyrene in tobacco smoke cite the reports of the incorrect compound.
 dibenzo[a,l]pyrene {dibenzo[def,p]chrysene}						
 dibenz[a,e]aceanthrylene						
indeno[1,2,3-*cd*]pyrene	✓ [4-20 ng]	✓	✓		no	
						

Table 4: Continued

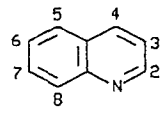
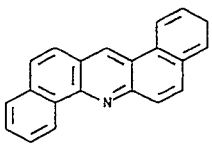
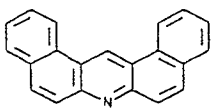
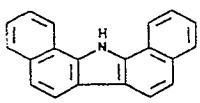
Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
			AZA-ARENES			
quinoline 	✓ [1-2 ng]		✓		no	
dibenz[*a,h*]acridine 	✓ [0.1 ng]	✓		✓	no	• The single value (0.1 ng/cigt) rather than a range indicates the MS level is based on a single report, that of Van Duuren *et al.* (1960a, 1960b), determined with existing cigarettes. • From 1961 through 1981 several groups of investigators have reported discordant results on the presence and/or levels of the aza-arenes dibenz[*a,h*]acridine, dibenz-[*a,j*]acridine, and 7*H*-dibenzo[*c,g*]-carbazole in cigarette MS. See discussion below.
dibenz[*a,j*]acridine 	✓ [3-10 ng]	✓		✓	no	
7*H*-dibenzo[*c,g*]carbazole 	✓ [0.7 ng]	✓		✓	no	

Table 4: Continued

Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
N-NITROSAMINES						
Hoffmann and Hecht (1990) did not acknowledge that the MS levels listed for both VNAs and TSNAs may be incorrect (and inflated) because of the artifactual formation of both types of NNAs during MS (and SS) collection as reported by Caldwell and Conner (1989, 1990). EPA accepted without question the MS VNA and MS TSNA delivery levels reported by Hoffmann and Hecht (1990). Presumably, OSHA personnel (OSHA, 1994) did likewise.						
N-nitrosodimethylamine (NDMA) CH_3 >N-NO CH_3	✓ [0.1-180 ng]	✓	✓		yes	• Lung tumor production via inhalation classified as "equivocal" by RTECS (1987). • Listed by OSHA (1994)[f] as a "probable human carcinogen."
N-nitrosoethylmethylamine CH_3CH_2 >N-NO CH_3	✓ [3-13 ng]		✓		no	
N-nitrosodiethylamine (NDEA) CH_3CH_2 >N-NO CH_3CH_2	✓ [ND-25 ng]	✓	✓		yes	• Lung tumor production via inhalation classified as "equivocal" by RTECS (1987). • Listed by OSHA (1994)[f] as a "probable human carcinogen."
N-nitrosodipropylamine (NDPA) $CH_3(CH_2)_2$ >N-NO $CH_3(CH_2)_2$	[ND-1.0 ng][d]	✓	✓		no	
N-nitrosodibutylamine (NDBA) $CH_3(CH_2)_3$ >N-NO $CH_3(CH_2)_3$	[ND-3 ng][d]	✓	✓		no	
N-nitrosopyrrolidine (NPYR) 	✓ [1.5-110 ng]	✓	✓		no	• Listed by OSHA (1994)[f] as a "probable human carcinogen."
N-nitrosodiethanolamine (NDELA) $HO(CH_2)_2$ >N-NO $HO(CH_2)_2$	✓ [ND-36 ng]	✓	✓		no	• The only precursor, the diethanolamine salt of maleic hydrazide added as a sucker control agent, in tobacco of *N*-nitroso-diethanolamine in tobacco smoke has been banned from use in USA tobacco agronomy since 1981 (EPA, 1981).

Table 4: Continued

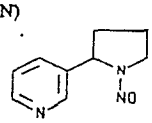
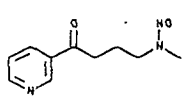
Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
			N-NITROSAMINES *(continued)*			
N-nitrosodiethanolamine (NDELA) *(cont.)*	✓ [ND-36 ng]	✓	✓		no	• The diminution of levels of *N*-nitrosodiethanolamine in tobacco should parallel the chronicled decrease in levels of arsenic and DDT in tobacco after these materials were no longer used in tobacco agronomy, *e.g.*, between 1968 and 1974, the residual level of DDT in USA flue-cured tobacco decreased from 52 μg/g in 1968 to 6 μg/g in 1970 to 0.23 μg/g in 1974 (USPHS, 1979; IARC, 1986). Similar decreases were reported for arsenic residues (Griffin *et al.*, 1975; USPHS, 1979; IARC, 1986). • Hoffmann *et al.* (1984a) predicted that *N*-nitrosodiethanolamine residues on tobacco (and in tobacco smoke) would decrease because of the 1981 ban on the use of the diethanolamine salt of maleic acid. • The IARC (1986) noted "Tobaccos grown in a [diethanolamine salt-free] environment and smoke generated from such tobaccos are devoid of *N*-nitrosodiethanolamine. • Listed by OSHA (1994)[e] as a "probable human carcinogen."
N'-nitrosonornicotine (NNN) 	✓ [0.12-3.7 μg]	✓	✓		no	• "[I]n contrast to NNK, NNN seldom induces lung tumors [when administered by non-inhalation routes]." (Hoffmann and Hecht, 1990). • Listed by OSHA (1994)[e] as an "animal carcinogen."
4-(*N*-methylnitrosamino)-1-(3-pyridinyl)-1-butanone (NNK) 	✓ [0.08-0.77 μg]	✓	✓		no	• "[NNK] has not been tested by inhalation." (Hoffmann and Hecht, 1990). • OSHA (1994)[e] commented that "relevant information [is] not available" on this compound.

Table 4: Continued

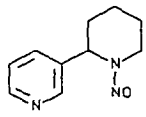
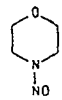
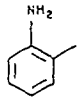
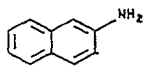
Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS Accepted	Presence in MS Controversial	Inhalation Toxicology: SCC[c] Production	Comments
			***N-NITROSAMINES** (continued)*			
N'-nitrosoanabasine 	✓ [0.14-4.6 ng]		✓		no	
N-nitrosomorpholine 	t [ND]		t		no	• Identified as a tobacco component but not identified to date as a tobacco smoke component[c].
N-nitrosopiperidine 	[ND-9][d]	✓	✓		no	
			AROMATIC AMINES			
2-toluidine {aniline, 2-methyl-} 	✓ [30-200 ng]	✓	✓		no	• IARC considers the evidence to classify 2-toluidine as a human carcinogen to be "inadequate," (*cf.* Hoffmann and Hecht, 1990). • "Recent studies have...shown that single ring aromatic amines, including the weak bladder carcinogen *o*-toluidine [2-toluidine], are present in human urine... The available data do not indicate that there are significant differences between smokers and nonsmokers." (Hoffmann and Hecht, 1990). • Listed by OSHA (1994)[c] as an "irritant, cardiovascular system."
2-naphthylamine 	✓ [1-22 ng]	✓	✓		no	• IARC (1974a) considers the evidence "sufficient" to classify 2-naphthylamine as a human carcinogen. • "An aromatic diamine...and 2-naphthylamine have also been reported in tobacco or tobacco smoke. The latter compound [2-naphthylamine] is a bladder

Table 4: Continued

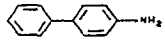
Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
			AROMATIC AMINES (continued)			
2-naphthylamine *(cont.)*	✓ [1-22 ng]	✓	✓		no	carcinogen in man..., but is present in cigarette smoke in amounts...too low to be considered a health hazard [Hoffmann *et al.*, 1969a]." (Schmeltz and Hoffmann, 1977). • "The presence of β-naphthylamine in cigarette smoke has been demonstrated..., along with other carcinogenic aromatic amines... The yield was so low that [the researchers] did not believe these agents contributed significantly to the risk of bladder cancer in smokers." (USPHS, 1981). • "On the basis of quantitative data for aromatic amines in cigarette smoke, an etiological significance of these traces of carcinogenic amines in bladder cancer is questionable, even if one were to consider the total of the aromatic amines and their metabolites..." (USPHS, 1982). • "[B]ecause [its] concentration in cigarette smoke is relatively low, there is uncertainty about [its] role in human bladder cancer induced by smoke." *Cf.* this statement with another in the same publication: "2-[N]aphthylamine [is one of the two] most likely cigarette smoke components to be involved in bladder cancer induction in smokers, according to presently available data."(Hoffmann and Hecht, 1990). • Listed by OSHA (1994)[e] as a "known human carcinogen."
biphenyl, 4-amino- 	✓ [2-5 ng]	✓	✓		no	• IARC (1972) considers the evidence "sufficient" to classify 4-aminobiphenyl as a human carcinogen. • "On the basis of quantitative data for aromatic amines in cigarette smoke, an etiological significance of these traces of carcinogenic amines in bladder cancer is questionable, even if one were to consider the total of the aromatic amines and their metabolites..." (USPHS, 1982). • "[B]ecause [its] concentration in cigarette smoke is relatively low, there is uncertainty

Table 4: Continued

Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
			AROMATIC AMINES (continued)			
biphenyl, 4-amino- *(cont.)*	✓ [2-5 ng]	✓	✓		no	about [its] role in human bladder cancer induced by smoke." *Cf.* this statement with another in the same publication: "4-Aminobiphenyl... [is one of the two] most likely cigarette smoke components to be involved in bladder cancer induction in smokers, according to presently available data." (Hoffmann and Hecht, 1990). • Listed by OSHA (1994)[e] as a "known human carcinogen."
			ALDEHYDES			
formaldehyde $H_2C=O$	✓ [70-100 μg]	✓	✓		no	• IARC (1982a) did not categorize formaldehyde as tumorigenic to humans.
acetaldehyde CH_3-CHO	✓ [18-1400 μg]	✓	✓		no	• Because of their water-solubility, large proportions of formaldehyde, acetaldehyde, and crotonaldehyde do not reach the lung because they are removed from orally-inhaled MS and ETS by "scrubbing" and from nasally-inhaled ETS by "resorption."
crotonaldehyde $CH_3CH=CH$-CHO	✓ [10-20 μg]		✓		no	
			MISCELLANEOUS ORGANIC COMPOUNDS			
benzene 	✓ [12-48 μg]	✓	✓		no	• Listed by OSHA (1994)[f] as a "known human carcinogen." • Benzene has been classified as an "A2 substance," *i.e.*, A suspected human carcinogen, not because of any tumorigenic property but because it is leukemogenic (IARC, 1974c, 1982b). None of the epidemiological studies on smoking shows any strong association between leukemia and cigarette smoking. • "Concern has been expressed in recent years about the possible risk of leukemia for workers who have been exposed to benzene... Although some prospective and retrospective studies [of smoking and disease] have reported a somewhat higher risk of leukemia for cigarette smokers, these data remain unconfirmed and no dose-response relationship has been established between death rate from leukemia and number of cigarettes smoked." (USPHS, 1979)

Table 4: Continued

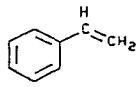
Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
			MISCELLANEOUS ORGANIC COMPOUNDS (continued)			
benzene *(cont.)*	✓ [12-48 μg]	✓	✓		no	• Numerous attempts to induce skin carcinoma via skin-painting experiments in a variety of species were singularly unsuccessful [*e.g.*, see Lignac, 1933; Hess, 1935; Bernard, 1936; etc. in Hartwell, 1951]. • In innumerable early studies (*cf.* Hartwell, 1951; Shubik and Hartwell, 1957, 1969; Thomas *et al.*, 1968/1969, 1970/1971) on the carcinogenicity of compounds such as PAHs, benzene was used as the solvent in skin-painting studies where several control groups [cage controls (no treatment), solvent controls (painted with solvent only), positive controls (known carcinogen in solvent), and experimental group (test material dissolved in solvent)] were treated with benzene or benzene solutions. Tumor development at the site of painting with benzene alone was a rarity; tumors at sites other than the painted area were also extremely rare. Subsequently, acetone replaced benzene as solvent of choice in many skin-painting studies. • Crabtree demonstrated that benzene, naphthalene, and anthracene (Crabtree, 1946) were highly effective anticarcinogens for BaP and DBA. Naphthalene and anthracene, identified PAHs in MS, are present in MS at levels far in excess of those for BaP, DBA, and the other PAHs listed by Hoffmann and Hecht (1990) and OSHA (1994).
styrene {benzene, ethenyl-} 		✓	✓		no	
acrylonitrile $H_2C=CH-CN$	✓ [3.2-15 μg]	✓	✓		no	• IARC (1979a) considered evidence "limited" to classify acrylonitrile as a human carcinogen. • "[I]ts role in tobacco carcinogenesis is difficult to evaluate due to lack of data." (Hoffmann and Hecht, 1990).

Table 4: Continued

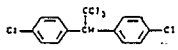
Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
MISCELLANEOUS ORGANIC COMPOUNDS (continued)						
hydrazine, 1,1-dimethyl- $(CH_3)_2N\text{-}NH_2$	✓ [?][h]	✓	✓		no	
propane, 2-nitro- $CH_3(CH_2)_2\text{-}NO_2$	✓ [0.73-1.21 µg]	✓	✓		no	• "[I]ts organospecificity for liver suggests that it does not play a major role in tobacco carcinogenesis." (Hoffmann and Wynder, 1990).
vinyl chloride $H_2C{=}CH\text{-}Cl$	✓ [1-16 ng]	✓	✓		no	• IARC (1979b) classified vinyl chloride as a human carcinogen. • "[I]ts low levels in cigarette MS do not support a major role in tobacco carcinogenesis." (Hoffmann and Hecht, 1990).
ethyl carbamate {urethane} $NH_2\text{-}COOCH_2CH_3$	✓ [20-38 ng]	✓	✓		no	• "[I]ts potential role in tobacco carcinogenesis is difficult to evaluate." (Hoffmann and Hecht. 1990). • Because of its water-solubility, a large proportion of ethyl carbamate does not reach the lung because it is removed from orally-inhaled MS and ETS by "scrubbing" and from nasally-inhaled ETS by "resorption."
DDT {ethane, 1,1,1-trichloro-2,2-*bis*(*p*-chlorophenyl)-} 		✓	✓		no	• Between 1968 and 1974, the residual level of DDT in USA flue-cured tobacco decreased from 52 µg/g in 1968 to 6 µg/g in 1970 to 0.23 µg/g in 1974 (USPHS, 1979; IARC, 1986). Similar decreases were reported for arsenic residues (Griffin *et al.*, 1975; USPHS, 1979; IARC, 1986). • Transfer rates of DDT from tobacco to MS have been reported at 5% (Nesemann *et al.*, 1968) and 12% (Hoffmann *et al.*, 1969b). With these % transfers and a DDT level of 0.23 µg/g tobacco, DDT in MS would range from about 11 to 28 ng/cigt. • Sufficient evidence to be considered carcinogenic to animals (IARC, 1986).

Table 4: Continued

Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
			INORGANIC COMPONENTS			
hydrazine H_2N-NH_2	✓ [24-43 ng]	✓	✓		no	• IARC (1974b) considered the evidence "inadequate" to classify hydrazine as a human carcinogen. • "[D]ata on hydrazine levels in cigarettes [*sic*] marketed in 1987 are not available." (Hoffmann and Hecht, 1990). • Because of its water-solubility, a large proportion of hydrazine does not reach the lung because it is removed from orally-inhaled MS and ETS by "scrubbing" and from nasally-inhaled ETS by "resorption."
arsenic As	✓ [40-120 ng]	✓	✓		no	• IARC (1980a) considered the evidence "sufficient" to classify arsenic as a human carcinogen. • In 1952, arsenicals were removed from the list of permitted insecticides for tobacco. By 1968, the arsenic content of USA tobacco had decreased from the 1951 level of about 50 μg/g to 0.5-1.0 μg/g (USPHS, 1979; IARC, 1986). In 1975, Griffin *et al.* (1975) reported tobacco arsenic levels in the range 0.5-0.9 μg/g. • Cogbill and Hobbs (1957) reported that a cigarette containing 7.1 μg of arsenic delivered 0.031 μg/puff (0.25 μg/cigt) in its MS, a transfer rate of 3.5%. A 2.5 pack-a-day smoker might inhale 12.5 μg/day of arsenic, *cf.* the report by Satterlee (1956) that an urban area (New York) atmosphere over a 12-year period showed an arsenic level of 100-400 μg/10 m^3, the approximate daily intake of a resident. If the arsenic level in its tobacco were 0.9 μg/g as reported by Griffin *et al.* (1975), a cigarette would deliver about 0.032 μg of arsenic in its MS.
nickel Ni	✓ [0-600 ng]	✓	✓		no	• IARC (1973) considered the evidence "limited" to classify nickel as a human carcinogen. • "It is not likely that nickel plays a significant role in the etiology of lung cancer in smokers." (USPHS, 1982).

Table 4: Continued

Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
			INORGANIC COMPONENTS (continued)			
nickel *(cont.)*	✓ [0-600 ng]	✓	✓		no	• Nickel listed by OSHA (1994)[e] as a "known human carcinogen."
chromium Cr	✓ [4-70 ng]	✓	✓		no	• IARC (1980b) considered the evidence "sufficient" to classify chromium as a human carcinogen. • "The possible [role] of chromium...in tobacco carcinogenesis [is] difficult to evaluate given the present data base." (Hoffmann and Hecht, 1990).
cadmium Cd	✓ [14-62 ng]	✓	✓		yes	• IARC considered the evidence "limited" to classify cadmium as a human carcinogen. • "The possible [role] of...cadmium...in tobacco carcinogenesis [is] difficult to evaluate given the present data base." (Hoffmann and Hecht, 1990). • Cadmium was listed by OSHA (1994)[e] as a "probable human carcinogen."
lead Pb	✓ [35-85 ng]	✓	✓		no	• IARC (1980c) considered the evidence "inadequate" to classify lead as a human carcinogen. • "The possible [role] of...lead...in tobacco carcinogenesis [is] difficult to evaluate given the present data base." (Hoffmann and Hecht, 1990).
polonium-210 ^{210}Po	✓ [0.03-1.0 pCi]		✓		yes	• "In the case of polonium-210, a recent indepth [*sic*] study raises doubts on the significance of ^{210}Po as a factor contributing to lung cancer in smokers..." (USPHS, 1981) • "[P]olonium-210 (^{210}Po) is present in tobacco and cigarette smoke (0.03 to 1.0 pCi/cigarette); however, it is unlikely these traces represent a major risk for the smoker... "From comparison of radon-daughter exposure of underground miners with their relative risk of lung cancer, Harley *et al.*

Table 4: Continued

Component	Listed in MS by H&H[b] (1990)	Listed in MS by OSHA (1994)	Presence in MS: Accepted	Presence in MS: Controversial	Inhalation Toxicology: SCC[c] Production	Comments
			INORGANIC COMPONENTS (continued)			
polonium-210 *(cont.)*	✓ [0.03-1.0 pCi]		✓		yes	(1980) deduced that ^{210}Po is a questionable risk factor for lung cancer in cigarette smokers..." (USPHS, 1982) • "[T]he quantities of polonium-210 found in the lungs of smokers are generally about three times higher than those in nonsmokers. However, the significance of polonium-210 in tobacco-induced lung cancer has been questioned upon comparison of these data with those obtained in miners (Harley *et al.*, 1980)." (Hoffmann and Hecht, 1990). • Listed by OSHA (1994)[e] as a "known human carcinogen."

[a] Table II-2 (OSHA, 1994)
[b] H&H = Hoffmann and Hecht. Values in square brackets are MS deliver ranges listed by Hoffmann and Hecht (1990); ND = not detected
[c] SCC = squamous cell carcinoma
[d] In only isolated instances has this NNA been reported as a component in the MS from nonfiltered cigarettes; it has not been reported in the MS from filtered cigarettes (Hoffmann *et al.*, 1984a)
[e] Table III-7 (OSHA, 1994)
[f] Table III-6 (OSHA, 1994)
[g] Listed as a tobacco component but not as a tobacco smoke component
[h] Hoffmann and Hecht (1990) listed no MS level for 1,1-dimethylhydrazine, but the Surgeon General (USPHS, 1979) listed an MS level of 100 ng/cigt

The misunderstanding and misinterpretation of these terms are not new. The term "carcinogenesis" and by extension derivative terms were defined precisely as early as 1923 and its original definition is still listed in various medical dictionaries: ***Carcinogenesis is the process whereby a carcinoma is generated.*** In the 27th edition (1988) of Dorland's medical dictionary, this definition of carcinogenesis is the same as that listed in the 13th edition (1927). The definition of "carcinogenesis," like the definition of some other terms in the medical-biological field, has been bastardized over the years by some who use the term to suit specific situations. Thus, some investigators incorrectly use the term "carcinogenesis" for the production of any tumor type not just a carcinoma. The correct term, if used in this manner, is "tumorigenesis." The term "carcinogen" is often applied, again often incorrectly, to any factor that induces any type of tumor. Common in the past, but seldom used now, was the term "sarcogenesis" used to describe the production of a sarcoma, the end-point obtained in many studies in which a PAH was injected subcutaneously.

Within 25 years of the first successful experiments to produce tumors in animals by skin painting with solutions of coal tar (Yamagiwa and Ichikawa, 1915, 1918, 1965) and within a

decade of the first successful skin tumor induction with pure compounds such as DBA (dibenz[*a,h*]anthracene) (Kennaway and Hieger, 1930) and BaP (benzo[*a*]pyrene) (Cook *et al.*, 1932, 1933), the misuse and misunderstanding of the term "carcinogenicity" had reached such proportions that Shear, an outstanding and highly regarded investigator in the field of carcinogenesis, was invited to write an article to put the term in perspective. The admonitions by Shear and Leiter (1941) of the dangers of misinterpretation and /or overinterpretation of these terms are as important today as they were when first published in 1941:

> [T]he term 'carcinogenic potency'...is not to be considered as an invariable property inherent in a compound but is merely a summary of the results of particular experiments and is valid only for animals of the species, strain, sex, age, diet, etc. of the particular animal employed as well as the dose, menstruum, mode and site of application, etc., of the compound in question... Conclusions regarding the potency of any given compounds should therefore be interpreted in the light of the data upon which they are based.

In 1951, Hartwell compiled the 2nd edition of a survey on the compounds that had been tested for carcinogenicity since the first demonstration of the carcinogenicity of DBA and BaP in the early 1930s. To further the understanding of the terms "carcinogen" and "carcinogenicity" to minimize their future misuse, Hartwell quoted liberally from the Shear-Leiter 1941 publication. He also added several important points, one of which was the following:

> There is a tendency on the part of some to consider carcinogenicity or lack of carcinogenicity as characteristic properties of chemical compounds.

In other words, some researchers treat carcinogenicity as a fixed property of a compound. This is not a valid approach to thinking about "carcinogens." Carcinogenicity is a variable property, depending on a number of factors. It differs from other properties of a compound that are fixed, *e.g.*, melting point, boiling point, refractive index, specific gravity, crystalline form. As noted by Shear and Leiter (1941), by Hartwell (1951), and by many others, a substance or factor can show a range from carcinogenicity to noncarcinogenicity to anticarcinogenicity and the response will differ in the laboratory depending on the animal used (species, strain, sex, age), route of administration [inhalation, ingestion, injection (subcutaneous, intravenous, intraperitoneal), skin painting, douching], mode of administration (single *vs* multiple doses, neat, in solution, as an aerosol or as a vapor), diet supplied the animals, and cage care.

Hartwell also wrote:

> Another pitfall is the attempt to carry over, without reservation, to man, conclusions based on animal experiments. We do not know whether man is more or less susceptible than mice to particular carcinogens. Some animal species, such as the rat, rabbit, and dog are much more resistant than is the mouse, and vice versa, while in the monkey none of the powerful carcinogens has been shown to produce tumors.

Some Comments on the "Lists of 43"

Examination of the two "Lists of 43" raises numerous questions as to why any of the

components are included in the lists at all.

First, the attempts to attribute the "carcinogenicity" of MS to a particular component are questionable. There are scores of citations over the past four decades from scientists and health organizations in which it is noted that no single component or class of components in MS acting either individually or in concert can explain observations in human smokers or in laboratory animals treated with heroic doses of MS. *E.g.*, comments on BaP or PAHs include those of J. W. Cook (1957) (who discovered BaP in 1932):

> [T]he tarry condensates of the smoke obtained by smoking cigarettes in machines...have 3,4-benzpyrene, but the amount is exceedingly small and there is considerable doubt about whether the concentration is high enough to produce carcinogenic action.

The U. S. Surgeon General (1981) stated:

> The contribution of BaP or PAH in general to mouse skin carcinogenesis by cigarette smoke condensate cannot be fully measured at this time...[I]n the smoking and health program of the National Cancer Institute...no significant dependence of carcinogenic potency on BaP content was observed.

and the American Association for Cancer Research in its 1984 position paper on smoking wrote:

> [S]tudies have presented the profile of the known carcinogens in tobacco [*sic*]. At present, there is no direct method to assign priority to any of these substances as putative causal agents in human lung cancer.

In 1985, Peto and Doll (who co-authored the Doll and Hill papers on epidemiology of smoking and lung cancer) stated:

> But 30 years of laboratory research has yet to identify reliably the important carcinogenic factors in cigarette smoke.

The U. S. Surgeon General (1982), on the subject of NNAs in tobacco smoke, stated:

> There is lack of direct evidence that these compounds are also human carcinogens.

This was also the view of Magee who, in the mid-1950s, first demonstrated the tumorigenicity of NNAs in laboratory animals. He noted in 1984:

> A role for nitrosamines in the causation of human cancer has not been established.

On the basis of the data available at the time, the aromatic amines, including β-naphthylamine, were discounted in the U. S. Surgeon General's 1981 and 1982 reports:

> The presence of β-naphthylamine in cigarette smoke has been demonstrated [Hoffmann *et al.*, 1969a], along with other carcinogenic aromatic amines [Patrianakos and Hoffmann, 1979]. The yield was so low that [the researchers] did not believe these agents contributed significantly to the

risk of bladder cancer in smokers. (USPHS, 1981)

On the basis of quantitative data for aromatic amines in cigarette smoke, an etiological significance of these traces of carcinogenic amines in bladder cancer is questionable, even if one were to consider the total of the aromatic amines and their metabolites. (USPHS, 1982)

Similar comments about other components on the "Lists of 43" are available: arsenic (USPHS, 1982), nickel (USPHS, 1982), polonium-210 (USPHS, 1981, 1982), and benzene (USPHS, 1979).

Many of these MS and/or tobacco components should be excluded from the list in **Table 4** on the basis of experimental evidence indicating their lack of tumorigenicity in laboratory animals treated with the levels determined in MS, their lack of tumorigenicity in most instances on inhalation, and the lack of evidence showing their tumorigenicity in humans at levels in MS.

Only five of the components listed have ever produced respiratory tract tumors in laboratory animals exposed to the component via inhalation. Many have never been tested in an inhalation system, and one component of great interest (BaP) has only produced lung carcinoma via inhalation in animals at an extraordinarily massive dose.

Results of inhalation studies are discussed briefly in a subsequent section.

The following point should not be overlooked: MS levels determined two to three decades ago for some of the components are not relevant to the MS levels that would be found if the analyses for these components were conducted on current or more recent cigarettes. MS values for dibenz[*a,h*]acridine and 7*H*-dibenzo[*c,g*]carbazole were obtained with 1959-1960 cigarettes, MS values for dibenz[*a,j*]acridine are from 1959-1960 and from 1963 cigarettes, the MS value for DBA is from 1963 cigarettes, the MS value for 5-methylchrysene is from 1973 cigarettes, and the MS value for *N*-nitrosodiethanolamine is from 1981 cigarettes. It is well recognized that a variety of cigarette design technologies [efficient filtration, filter-tip additives, processed tobacco materials (RTS, expanded tobaccos), air dilution (porous paper, filter-tip perforations), and paper additives] has progressively reduced the sales-weighted average MS TPM by almost 70% from 40 mg/cigt in the early 1950s to less than 12 mg/cigt in the late 1980s. At the same time that the reduction of delivery of MS TPM was accomplished, the composition of the MS was altered. *E.g.*, for MS TPM, the BaP content — expressed as ng BaP/mg TPM — has decreased about 33% (from 1.2 ng/mg TPM to 0.8 ng/mg TPM) during the same time period. The 1979 Surgeon General's report (USPHS, 1979) summarizes the BaP data for a commercial cigarette sold in the USA from 1954 to 1979. The decrease in cigarette nicotine content and delivery over the same time period will also have influenced the pyrogenesis of the dibenzacridines and dibenzocarbazole during tobacco smoking.

Numerous compounds demonstrated in various animal studies to be highly effective anticarcinogens against many of the MS components in both "Lists of 43" have been identified in tobacco smoke at levels far in excess of the alleged carcinogens. Seldom are these MS components discussed in reviews of the chemistry and biological properties of MS.

The number of anticarcinogens and inhibitors identified in cigarette MS exceeds the number of "tumorigens" listed in **Table 4.** Many of them are present in MS at levels far in excess of the levels of several of the alleged "tumorigens," *e.g.*, the anticarcinogens α-tocopherol *vs* BaP; phenanthrene *vs* BaP; and β-sitosterol *vs* BaP, and the inhibitor saturated aliphatic hydrocarbon fraction *vs* BaP. A list of anticarcinogens and inhibitors with discussion of their smoke level and reported action is provided in the text accompanying **Table 32.** One of the compounds in the "Lists of 43" (benzene) has been shown to be a highly effective anticarcinogen against BaP and DBA. In fact, benzene was one of the earliest compounds demonstrated to be anticarcinogenic against any PAH.

Reasons to Exclude Various Components Included in the "Lists of 43"

In **Table 4,** some information was provided on many components in the two "Lists of 43" which raises serious questions as to why they were included. Other information has been available for many years on a number of the components listed which makes it even more obvious why almost all the components could and should be removed from the lists.

Of the components in the Hoffmann-Hecht and OSHA lists, the three classes of tobacco smoke components investigated in the greatest detail during the past four decades are the PAHs, the aza-arenes, and the NNAs. Because of the wealth of background information available on PAHs demonstrated to be tumorigenic in laboratory animals, extensive research (isolation, identification, quantitation, precursors, removal, prevention of formation, etc.) was conducted in the 1950s and 1960s on this compound class in tobacco smoke. The reason for selection of this class of compounds was obvious.

In the early 1930s, Kennaway and Hieger (1930) were the first to demonstrate the tumorigenicity to mouse skin of DBA, a PAH prepared synthetically. Two years later, Cook *et al.* (1932, 1933) demonstrated similar tumorigenicity of the coal-tar isolate, BaP. Later, Barry *et al.* (1935) reported the tumorigenicity to mouse skin of several azar-arenes, dibenzacridines structurally similar to the tumorigenic dibenzanthracenes. During the next two decades, hundreds of polycyclic compounds — both PAHs and aza-arenes — were synthesized and their tumorigenicity determined in laboratory animals.

It has been estimated that more research funds have been expended since the 1930s on the study of tumorigenic polycyclic compounds in general (and BaP in particular) than on any other class of compounds. The results of thousands of studies on PAHs [synthesis, biological properties (tumorigenicity, mutagenicity), metabolism, sources (air pollutants, industrial oils and tars, tobacco smoke, foodstuffs, beverages, etc.), isolation, quantitation, reduction, etc.] have been published. Similar studies, but to a lesser degree, were conducted with the aza-arenes. Since the early 1950s, nearly a thousand PAHs and three hundred aza-arenes have been reported as tobacco smoke components. The per cigarette deliveries of most of the PAHs and aza-arenes are in the subnanogram range.

In the early 1950s, the discovery of the tumorigenicity (Barnes and Magee, 1954) of an

NNA in laboratory animals initiated a flurry of research on the NNAs initially in foodstuffs and subsequently (mid-1960s) in tobacco smoke. In contrast to the great number of PAHs and aza-arenes identified in tobacco smoke, fewer than forty NNAs have been identified in tobacco and/or tobacco smoke to date.

Nearly 60% of the components considered significant tumorigens in tobacco smoke by Hoffmann and Hecht (1990) and OSHA (1994) comprise the PAHs, the aza-arenes, and the NNAs. Both the OSHA 1994 list and the Hoffmann-Hecht/EPA 1990 list include 11 PAHs, nine of which are common to both lists. **Table 5** summarizes the situation in the two lists with regard to these three much studied classes of MS components.

TABLE 5: COMPARISON OF THE TWO "LISTS OF 43" TUMORIGENS

Listed Tumorigen	Hoffmann and Hecht (1990) and EPA (1990)	OSHA (1994)	Total in Both Lists	Common to Both Lists
Total listed	43	43[a]	50	35
PAHs	11 (25.6)[b]	11 (25.6)	13 (26.0)	9 (25.7)
Aza-arenes	4 (9.3)	3 (7.0)	4 (8.0)	3 (8.6)
NNAs	9[c] (21.0)	9 (21.0)	12 (24.0)	6 (17.1)
Total in 3 classes	24 (55.8)	23 (53.5)	29 (58.0)	18 (51.4)

[a] The title of Table II-2 (OSHA, 1994) claims *43 Chemical Compounds Identified in Tobacco Smoke for Which There Is "Sufficient Evidence" for Carcinogenicity in Humans or Animals* but only 42 components are listed. It is suspected that polonium-210 was inadvertently omitted from the OSHA list. Calculations are based on 43, not 42 OSHA-listed components.

[b] Number in parentheses represents %.

[c] One NNA, NMOR, in the Hoffmann-Hecht list has been identified in tobacco but not in tobacco smoke.

Examination of these three classes of tobacco smoke components, representing nearly 60% of the components appearing on the two "Lists of 43," reveals several interesting facts.

The Polycyclic Aromatic Hydrocarbons (PAHs)

In the case of the PAHs in general and the thirteen specific PAHs, including BaP, listed by Hoffmann and Hecht (1990) and OSHA (1994) (see **Table 4**), almost every assertion about them in tobacco smoke since the early 1950s has either been shown to be incorrect or, in some instances, highly equivocal.

Examples of these assertions include:

- Several sources of PAHs in cigarette MS, originally considered to be the *major* sources of the PAHs, were shown to be either incorrect, *e.g.*, effluents from lighting source (matches, butane or hexane-fueled lighters) or insignificant, *e.g.*, PAH-

containing air pollutants deposited on the surface of the tobacco leaf during growing, harvesting, etc., cigarette paper combustion.

- Initially, long-chained saturated hydrocarbons were incorrectly defined as the *major* precursors in tobacco of PAHs in tobacco smoke. Subsequently, it was shown that the contributions of tobacco terpenes and phytosterols to the levels of MS or SS PAHs far outweighed those of the saturated hydrocarbons in tobacco.

- In the late 1950s, it was proposed that the level of MS PAHs could be diminished by *removal* of saturated hydrocarbons, phytosterols, and terpenes from the tobacco by extraction with nonpolar solvents such as hexane, a process dubbed the "dry cleaning" of tobacco[c]. It was proposed that the reduced MS PAH level from cigarettes fabricated with extracted tobacco would be accompanied by reduced tumorigenicity to mouse skin of the extracted tobacco MS CSC. More recently — in the early 1980s, one of the same research groups that advanced the original proposal to remove the wax-like compounds considered the precursors of the PAHs in smoke advocated the *addition* of such compounds!

- Also in the late 1950s, it was proposed to use *high-nitrate* tobacco in the tobacco blend or *add* nitrate to the blend to modify the combustion process during smoking with a subsequent decrease in MS PAH levels. In direct contrast was the proposal advanced in the early 1980s: Because of the involvement of nitrate and nitrogen oxides generated from it in the pyrogenesis of NNAs, use *low-nitrate* tobaccos in the blend or *remove* the nitrate from tobacco as a means to control NNAs in MS (and SS).

- The proposal that high molecular weight PAHs, including BaP, can be removed from MS by selective filtration was shown to be incorrect. Selective filtration from MS is possible only with compounds that have an appreciable vapor pressure, *i.e.*, they are found in both the particulate and vapor phases of MS. *E.g.*, the low molecular weight phenols and the volatile NNAs are sufficiently volatile to be selectively filtered from MS, but the vapor pressures of most PAHs of interest (BaP, DBA, BA) are too low for selective filtration to be effective.

- BaP in MS was proposed as an "indicator" of (a) the tumorigenicity of CSC to mouse skin, (b) the level of PAHs with four or more rings, and (c) the levels of tumorigenic PAHs. In none of these cases is the level of BaP a valid "indicator." (Similarly, phenol, proposed as an "indicator" of the level of low molecular

[c] Extraction of tobacco with an organic solvent to remove PAH precursors was not a new concept. Roffo (1942) reported that extraction of tobacco with organic solvents such as ethyl alcohol, chloroform, acetone, petroleum ether, paraffin hydrocarbons, or benzene resulted in a reduction of the tumorigenicity of the tar generated by *destructive distillation* of the extracted tobacco compared to the tar generated by *destructive distillation* of the unextracted (control) tobacco. Roffo did not study the smokes from cigarettes fabricated with the extracted and unextracted tobaccos. He suggested that the extraction removed the phytosterols from the tobacco which he considered the major precursor of the PAHs in the destructive distillate and in tobacco smoke.

weight phenols in cigarette MS, was shown not to be a valid "indicator.")

- Claims that alkylated PAHs (methyl- and dimethyl-PAHs) could not occur in tobacco smoke were demonstrated to be incorrect. Subsequently, even polyalkylated PAHs such as pentamethyl- and hexamethyl-PAHs have been identified in tobacco smoke, their major precursor being the high molecular weight tobacco terpenes such as solanesol.

- Claims that cyclopentabenzanthracenes could not occur in tobacco smoke were demonstrated to be incorrect. Numerous cyclopentabenzanthracenes have been identified in MS, their major precursor being the phytosterols.

- PAHs in tobacco smoke are formed either by (a) a degradation-combination mechanism or (b) an aromatization mechanism involving a single molecule. Studies showed that both mechanisms are operative.

- To bolster several arguments concerning PAHs in MS, it was incorrectly claimed by some anti-tobacco smoking investigators that the fate of an individual tobacco component during experimental pyrolysis was the same as its fate in the tobacco matrix during the smoking process in a cigarette. This was shown to be incorrect by numerous investigators, including personnel from the same laboratory that advanced the original proposal of the equivalency of the fate of tobacco components during pyrolysis and the smoking process.

- The tumorigenicity of CSC to mouse skin is due to its content of PAHs with four or more fused rings. Even though it is claimed that the PAHs are the only initiators in CSC, their level in CSC can account for no more than 2% of the observed tumorigenic response in mouse or other rodent skin-painting studies.

With so many incorrect or equivocal proposals on the MS PAHs issued by the anti-tobacco smoking investigators over the last four decades (see **Table 6**), it is somewhat surprising that either OSHA or EPA is so willing to accept the premise that the thirteen PAHs in the two "Lists of 43" contribute significantly to the alleged tumorigenic effects of MS and ETS in the respiratory tract of active and passive smokers, respectively.

TABLE 6: THE POLYCYCLIC AROMATIC HYDROCARBON PARADOXES

Proposal	*Contradiction*
§ Major source of PAHs[a] in cigarette MS is lighting source (match, flammable fuel-charged lighter, gas burner in laboratory) which generated PAHs from combustion of organic material in the match, lighter fluid, or gas.	§ PAH level in cigarette MS was independent of lighting source: Cigarettes lit by an electric lighter gave the same PAH levels as those lit by matches, fuel-charged cigarette lighters, or a gas flame.
§ Bulk pyrolysis of cigarette paper yields PAHs in the pyrolysate; thus, cigarette paper (representing about 5% of the cigarette weight) is the major source of the PAHs in MS (Cooper *et al.*, 1955; Cardon *et al.*, 1956).	§ Comparison of amounts of PAHs, including BaP, produced by bulk pyrolysis of cigarette paper *vs* pyrolysis of the paper in a cylindrical form approximating its configuration in the cigarette revealed that the cylindrical configuration combustion produced very little PAHs (or BaP) *vs* the bulk pyrolysis (Wright, 1957a).
§ Cigarette MS PAHs are the result of transfer of PAHs from the surface of air pollutant-contaminated tobacco to MS.	§ MS PAH level was not due to transfer of contaminant PAHs transfer from the tobacco rod to smoke: BaP injected into the tobacco rod produced very little increase in the MS BaP level. Most of the injected BaP was destroyed during smoking process.
§ Since none of the factors noted above (means of cigarette lighting, cigarette paper, air pollutant contamination) is the source of PAHs in tobacco smoke, the source must be one or more tobacco components. However, the presence of BaP in tobacco smoke was questioned [*cf.* Fieser (1957)].	§ Because of the fragmentary evidence presented, the presence of PAHs, particularly BaP, in tobacco smoke was questioned by such noted PAH experts as Fieser (1957) whose colleagues could identify BaP in roasted coffee beans but not in tobacco smoke. Eventually, the evidence became so firm that the presence of BaP in tobacco smoke is universally accepted.
§ The PAHs are only major tumor initiators in mouse skin carcinogenesis (Wynder and Hoffmann, 1967): The many detailed data obtained in studies of tobacco carcinogenesis on mouse skin exclude with some certainty that major tumor initiators other than the PAH type play a role in this assay system. BaP, because of its potency in skin-tumor carcinogenesis and level in MS, was considered the major PAH of concern in tobacco smoke. In the 1981 Surgeon General's report (USPHS, 1981), it is stated:	§ Mouse skin-painting studies with BaP solutions at concentrations much in excess of that in MS CSC produced no skin carcinomas in rabbits or mice (Wynder *et al.*, 1957; Warshawsky *et al.*, 1993). Similarly, use of more reasonable doses of CSC in skin-painting studies instead of the massive doses usually used resulted in neither papilloma nor carcinoma formation (Wynder *et al.*, 1957a, 1957b; Gori, 1976a, 1976b, 1977, 1980; NCI, 1980).

Table 6: Continued

Proposal	*Contradiction*
Continued:	*Continued:*
[Benzo[*a*]pyrene] appears to be the most important single member of this class of compounds [the polycyclic aromatic hydrocarbons], taking into consideration both its concentration and its relative carcinogenic potency.	
§ Initially, Fieser did not believe the evidence was sufficient to demonstrate that BaP was present in tobacco smoke. He stated that if BaP were present, its precursor would be the cellulose in the tobacco (Fieser, 1957).	§ Subsequent studies indicated that the major precursors in tobacco of PAHs in its smoke were not the biopolymers cellulose and lignin but were the lipophilic components of tobacco.
The major precursors of the PAHs in cigarette smoke are the high molecular weight lipophilic components of tobacco, *e.g.*, saturated aliphatic hydrocarbons, terpenoid compounds, phytosterols.	
Various investigators (Lam, Wright, Wynder) had different views as to the importance of each precursor, even though they were collaborators. Wright favored terpenoid compounds and phytosterols, Lam favored saturated hydrocarbons, Wynder favored saturated hydrocarbons and phytosterols. Their collaborative reports usually emphasized Wynder's point-of-view!	Rodgman and Cook (1965) and Severson *et al.* (1979) reported that the three classes of compounds — terpenoids, phytosterols, and saturated hydrocarbons — were PAH precursors with the terpenoid compounds, *e.g.*, solanesol, and the phytosterols being the most important.
§ Removal of lipophilic PAH precursors from tobacco by solvent extraction reduces the MS PAH levels and the tumorigenicity (mouse skin-painting) of the MS CSC (Wynder, 1956; Wright, 1957b; Wynder and Wright, 1958a, 1958b). *This led to their recommendations to remove the lipophilic components from tobacco.*	§ Biological activity of MS CSC from the extracted tobacco was decreased but to a much lesser extent than the MS PAH (and BaP) decrease. This result occurred because of two unanticipated effects of extraction on the tobacco and its smoke:
Later, Wynder *et al.* (1967) minimized the effectiveness of the removal of the lipophilic tobacco components. Wynder and Hoffmann (1960) ruled out tobacco extraction as being "impractical both technically and economically." Wynder and Hecht (1976) and the Surgeon General (USPHS, 1979) described tobacco extraction as "of academic interest."	• Extracted lipophilic compounds included various inhibitors (saturated hydrocarbons) and anticarcinogens (α-tocopherol, β-sitosterol, cholesterol, *D*-limonene, duvanediols) which have been reported to offset the tumorigenicity of PAHs. • Residual tobacco after extraction contains higher levels of lignin, cellulose, and pectins, all of which generate promoting/-

Table 6: Continued

Proposal	*Contradiction*
Continued:	*Continued:*
Eventually, Wynder's colleagues *recommended the addition of lipophilic compounds* (e.g., n-*hentriacontane) to tobacco* (Brunnemann and Hoffmann, 1982) to offset effect of nitrate-derived nitrogen oxides in NNA formation.	cocarcinogenic phenols during smoking process: Levels of low molecular weight phenols in MS are increased.
§ PAHs in cigarette smoke by one or other of the following mechanism: • Organic compounds in tobacco are degraded to simpler molecules during the pyrolysis processes occurring in the burning cigarette and these simpler molecules recombine to PAHs (degradation-combination mechanism) [*cf.*, Badger *et al.*, (1965, 1966) and earlier papers]. • During the pyrolysis processes occurring in the burning cigarette, high molecular weight compounds in tobacco undergo unimolecular cyclization, dehydration, aromatization, ring expansion , etc. to form PAHs (aromatization reaction) (Rodgman and Cook, 1965).	§ The mechanism of PAH formation is not an either-or situation. Laboratory data indicate that both mechanisms are operative in PAH formation in the burning cigarette. Evidence for the unimolecular aromatization reaction was provided by pyrolysis data and cigarette "spiking" data with phytosterols. In this instance, the relatively high levels of chrysene and cyclopentaphenanthrene *vs* BaP are more readily explained by the unimolecular aromatization of the tetracyclic sterol.
§ Inhaled cigarette smoke is the responsible agent for respiratory tract cancer, particularly squamous cell carcinoma of the lung, in smokers. It was implied in the late 1950s and in the 1960s that the responsible agent in MS may be the PAHs, particularly BaP.	§ Inhalation experiments with laboratory animals exposed for their lifetime to cigarette smoke have consistently failed to produce pulmonary squamous cell carcinoma (Essenberg, 1952, 1954b, 1957; Leuchtenberger *et al*, 1958, 1960a, 1960b, 1962; Henry and Kouri, 1984, 1986), the lung tumor type reported to be associated with smoking in humans. Similar exposures of laboratory animals to vehicular exhaust gases produced pulmonary squamous cell carcinoma (Mauderly *et al.*, 1987). Inhalation studies with BaP at levels comparable to those in cigarette smoke have consistently been negative. Tumor production at extremely high levels of inhalation exposure to BaP were described as "equivocal" (RTECS, 1987).

Table 6: Continued

Proposal	*Contradiction*
	Continued:
	From a study with roofers exposed via inhalation to levels of BaP equivalent to the daily inhalation of the MS from over 700 cigarettes, Selikoff *et al.* (1969) concluded: [I]f a high level of exposure to benzo[*a*]pyrene has any relation to lung cancer, the effect must be small... [I]f a high level of occupational exposure to benzo[*a*]-pyrene by way of inhalation results in little if any increase in the risk of lung cancer — then it seems unlikely that the extremely small amount of benzo[*a*]-pyrene in cigarette smoke can account for the high degree of association between cigarette smoking and lung cancer.
§ Since BaP and other known tumorigenic PAHs account for so little (< 2%) of the observed biological effect in mouse skin-painting studies, there are two possibilities: A PAH whose tumorigenicity is equivalent to that of BaP is present at a substantially higher level (25 to 50 times) than BaP or there is an unknown "supercarcinogenic" PAH in CSC, present at a level similar to that of BaP but whose activity is 25 to 50 times that of BaP (Wright, 1957).	§ After a year and a half unsuccessful search, attempts to find either the highly tumorigenic PAH present at a high level or the "supercarcinogenic" PAH were discontinued (Wright). Neither of these proposals has resurfaced since the late 1950s.
§ Since BaP in CSC acting alone accounts for less than 2% and the total PAH fraction accounts for less than 3% of the observed biological response in mouse skin-painting studies and no "supercarcinogenic" PAH is present, additional mechanisms are needed to explain the biological effect: The mechanisms of promotion and cocarcinogenesis of tobacco smoke components (phenols, etc.) may explain the observed effect in skin-painting studies with CSC.	§ The promoting/cocarcinogenic effect of phenols on PAH tumorigenicity was offset by the following: • Removal of the low-molecular weight phenols by selective filtration of smoke "does not change significantly the biological activity of the resulting condensate." (Hecht *et al.*, 1974c, 1975). • Phenols inhibited the tumorigenicity of PAHs such as BaP (Van Duuren *et al.*, 1971, 1973). • Inclusion of known initiators, promoters, and cocarcinogens in tobacco smoke in the calculation explained less than 5% of the observed biological effect in skin-painting studies.

Table 6: Continued

Proposal	*Contradiction*
§ Wynder and Hoffmann (1963b) reported that doubling the level of tumorigenic 17 PAHs in CSC produces "a statistically significant increase in tumor yield."	§ Increasing the BaP level in CSC by a factor of 10 produced no increase in the tumorigenicity of CSC (Roe, 1962, 1963); increasing the level of BaP by a factor of 30 produced no increase in the tumorigenicity of the CSC in mouse skin-painting studies (Lazar *et al.*, 1966a, 1966b).
§ The BaP level in CSC is an "indicator" or "marker" of the following: • The levels of the tetracyclic and higher PAHs, particularly those that are tumorigenic. • The tumorigenicity of the cigarette smoke condensate in mouse skin-painting studies.	§ Ample evidence indicated these premises are invalid: • No significant correlation between levels of BaP and other PAHs in pyrolysates from pyrolysis studies (Lam, 1955, 1956). • Contradictory data provided from the studies of Wynder *et al.* (1958a, 1958b, 1959), Campbell and Lindsey (1956), and Severson *et al.* (1979). • No significant correlation between levels of BaP and chrysene (Rodgman and Cook, 1965) or BaP and BaA (Gori, 1976a, 1976b, 1977, 1980) in cigarette smoking studies. • No significant correlation between tumorigenicity of over 130 test and reference CSCs to mouse skin and their BaP and/or BaA content (Gori, 1976a, 1976b, 1977, 1980). • In non-CSC-related studies, Warshawsky *et al.* (1993) found in their study of the carcinogenic potential of mixtures that the carcinogenic "activity" of a mixture cannot be accounted for by the level of BaP present."
§ Tumorigenicity of PAHs, *e.g.*, BaP, is inhibited by representative hydrocarbons ($C_{31}H_{64}$ and $C_{35}H_{72}$) in the saturated hydrocarbon (SHC) fraction of CSC at SHC:BaP ratios much less than that found in CSC (Wynder and Hoffmann, 1961a, 1961b, 1962b).	§ Inhibitors and anticarcinogens more potent in their effect against PAHs than the saturated hydrocarbon fraction in mouse skin carcinogenesis have been identified in CSC (phytosterols, α-tocopherol, duvanediols, limonene): Their concentrations relative to that of the PAHs are far in excess of that required to elicit anticarcinogenesis.
§ Reports of the presence of 7,12-dimethylbenz[*a*]anthracene in MS CSC (Pietzsch, 1959;	§ Snook *et al.* (1977, 1978) reported the identification of numerous alkyl-, dialkyl-, and

Table 6: Continued

Proposal	*Contradiction*
Continued:	*Continued:*
Kröller, 1964) were criticized because "the formation of a dialkylated benz[*a*]anthracene during pyrolysis appears questionable" (Cook, 1961; Wynder and Hoffmann, 1967).	multialkylbenz[*a*]anthracenes from MS CSC. Subsequent research indicated a host of mono- to pentaalkyl-PAHs in MS CSC. Their major precursors are the terpenoid compounds in tobacco, *e.g.*, solanesol, neophytadiene.
§ Report of presence of 1,2-dihydro-3-methylbenz[*j*]aceanthrylene (3-methylcholanthrene) in CSC (Kröller, 1964) was criticized by Wynder and Hoffmann (1967): "Since this carcinogenic hydrocarbon has not yet been found in any other combustion product, it remains a doubtful assumption that it is present in tobacco smoke..."	§ Several benzo[*a*]cyclopentanthracenes, structurally similar to 1,2-dihydro-3-methylbenz[*j*]aceanthrylene (3-methylcholanthrene, a methylbenz[*a*]cyclopent-[*fg*]anthracene) have been identified in CSC: These include the unmethylated 1,2-dihydrobenz[*j*]-aceanthrylene (cholanthrene) (Rodgman and Cook, 1965), 2,3-dihydro-1*H*-benzo[*a*]cyclopent[*h*]-anthracene (Bonnet and Neukomm, 1956, 1957, 1959a, 1959b; Ahlmann, 1958; Bonnet, 1958; Pyriki, 1963; Rodgman and Cook, 1965) and 9,10-dihydro-9*H*-benzo[*a*]cyclopent[*j*]anthracene (Bonnet and Neukomm, 1956, 1957, 1959a, 1959b; Ahlmann, 1958; Bonnet, 1958; Pyriki, 1963; Rodgman and Cook, 1965).
§ Dibenzo[*a,l*]pyrene is present in CSC and the pyrolysate from saturated tobacco hydrocarbons (Wynder *et al.*, 1958a, 1958b). It was identified on the basis of the agreement between spectral data for the isolate and those described in the literature for a synthetic hydrocarbon (Lyons and Johnston, 1957; Lyons, 1958, 1962; Wynder and Wright, 1957; Rodgman and Cook, 1965; Pyriki, 1962, 1963; Bonnet and Neukomm, 1959a, 1959b).	§ Lavit-Lamy and Buu-Hoï (1966) demonstrated that the synthetic PAH originally defined as dibenzo[*a,l*]pyrene (dibenzo[*def,p*]chrysene) and spectrally identical with the tobacco smoke isolate was actually dibenz[*a,e*]aceanthrylene (dibenzo[*a,e*]fluoranthene), a fact accepted by Hoffmann and Wynder (1968). Dibenzo[*def,p*]-chrysene (dibenzo[*a,l*]pyrene) was subsequently identified in tobacco smoke by Snook *et al.* (1977), but no quantitative data were reported. In citations of dibenzo[*a,l*]pyrene as one of the "tumorigenic agents in tobacco smoke," Hoffmann and Hecht (1990), the IARC (1985, 1986), and the EPA (1990) indicated only that the PAH was "present." Whether its "presence" was based on the erroneous dibenzo[*a,l*]pyrene reports from the 1950s or the bonafide dibenzo[*a,l*]pyrene report of Snook *et al.* (1977) is unclear.
§ Addition of nitrate to the tobacco blend significantly reduces the levels in MS of "tar," PAHs, and	§ Reductions in these deliveries were confirmed (Rodgman and Cook, 1965), but they were less than

Table 6: Continued

Proposal	*Contradiction*
Continued:	*Continued:*
phenols. The odd-electron compound nitric oxide generated during the smoking process interrupts the free radical mechanism of formation of PAHs (Hoffmann and Wynder, 1967).	those originally proposed. In fact, in the first NCI-TWG study (Gori, 1976a), doubling the nitrate level produced the following changes: "Tar", -7%; phenanthrene, -9%; BaP, +23%; BaA, -17%; phenol, -10%; nitric oxide; +111%.
The tumorigenicity (% tumor-bearing animals) of the resulting CSC is also reduced by about 80%. On the basis of these results, nitrate *addition* or use of *high*-nitrate tobaccos was proposed.	Doubling the nitrate level decreased the tumorigenicity (% tumor-bearing animals) by about 20%.
	Later data showed that increasing the nitrate increases both the volatile NNAs and TSNAs in the smoke. This led to the proposal to *remove* nitrates or use *low*-nitrate tobaccos (Brunnemann and Hoffmann, 1982). However, Hoffmann and Hecht (1990) included these NNAs in their list of "tumorigenic agents in tobacco smoke."
§ Increasing the number of cuts/inch (decreasing the cut width) for the tobacco filler reduces the delivery of CSC and BaP (Hoffmann and Wynder, 1963).	§ The 1967 Hoffmann-Wynder findings were not confirmed either at RJRT or in the NCI-TWG study (Gori, 1976a): In the latter study, the BaP and BaA deliveries for the normal filler cut (32 cpi) were less than those for the coarse (20 cpi) and fine (60 cpi) cuts.
§ PAHs are removed selectively by filters treated with reagents (chloranil, picric acid, 2,4,7-trinitrofluorenone) that form stable complexes with PAHs (Szent-Gyorgi, 1960).	§ Complexing reagents such as chloranil or 2,4,7-trinitrofluorenone did not selectively reduce the MS levels of PAHs (Rodgman and Cook, 1965). The complexing agent is unable to react with the nonvolatile PAHs in the milieu of thousands of compounds in the particles of the smoke aerosol.
§ Because of the nature of the cigarette smoke aerosol, Wynder and Hoffmann (1961a) considered selective filtration of a specific smoke component or class of smoke components such as the PAHs to be an "impossibility." Selective filtration is not "impossible" (Wynder and Hoffmann, 1962b).	§ Wynder and Hoffmann (1962b) reversed their view on the impossibility of selective filtration when they found that relatively volatile smoke components, *e.g.*, low molecular weight phenols, are selectively removed from the MS by filters incorporating certain plasticizers, *e.g.*, triacetin (*cf.*, Laurene *et al.*, 1963). Some years later, the same phenomenon was observed with volatile NNAs (Fredrickson, 1965/1967; Brunnemann *et al.*, 1977).
§ Single compound pyrolysis at 800°C in an inert atmosphere (nitrogen or helium) is equivalent to the conditions existing in a smoked cigarette (Wynder and Hoffmann, 1964, 1967). This proposal was originally an attempt to justify drawing conclusions	§ On the basis of numerous laboratory data, this premise was criticized by several investigators (Bell *et al.*, 1966; Benner *et al.*, 1969a, 1969b; Schlotzhauer and Schmeltz, 1969a, 1969b; Chortyk and Schlotzhauer, 1973; Baker, 1976, 1979, 1980,

Table 6: Continued

Proposal	*Contradiction*
Continued:	*Continued:*
on PAHs in MS on the basis of pyrolysis data.	1987a, 1987b; Baker and Robinson, 1990). Proponents of the equivalence of inert-atmosphere pyrolysis of a tobacco component and its behavior in a burning cigarette during the smoking process misinterpret one set of data and disregard another: • The atmosphere immediately behind the burning coal is oxygen-deficient compared to the oxygen level of the air entering the cigarette at the lit end and the smoke exiting the cigarette at the mouthend but it is *not* oxygen-free. • The oxygen level in the tobacco rod a short distance (1-2 mm) behind the tobacco rod-fire cone interface is influenced by diluting air entering the tobacco rod through the cigarette paper and this diluting air increases as the cigarette paper porosity increases. The ultimate contradiction was provided from the laboratory of the original claimants. Schmeltz, Wenger, Hoffmann, and Tso (1979) reported that the fate of radiolabeled nicotine on pyrolysis was entirely different from its fate in the smoking process: > These results suggest to us that pyrolysis experiments may be of limited value for establishing the fate of nicotine *and possibly other tobacco components* in a burning cigarette. (*Emphasis added*)
§ Severson *et al.* (1979) describe "the pyrolytic conditions that yielded [polycyclic aromatic hydrocarbon] profiles of tobacco pyrolyzates that could be correlated with [cigarette smoke condensate] profiles...."	§ The anticipated correlation was not attained: When the tobacco, a tobacco extract, and the residual extracted tobacco were pyrolysed, neither the amounts obtained for the individual PAHs **other than BaP**, the phenols, nor the acids (volatile or nonvolatile) in the tobacco pyrolysate matched the totals of the amounts in the extract pyrolysate plus the amounts in the residual tobacco pyrolysate. For the individual PAHs **(except for BaP)** and the acids, the totals of the amounts from the extract pyrolysate

Table 6: Continued

Proposal	*Contradiction*
	Continued:
	plus residue pyrolysate were higher than the amounts from the tobacco pyrolysate. For the individual phenols, the opposite was the case: The totals were less!

[a] PAH = polycyclic aromatic hydrocarbon; MS = mainstream smoke; SS = sidestream smoke; CSC = cigarette smoke condensate; BaP = benzo[*a*]pyrene; BaA = benz[*a*]anthracene; NNA = *N*-nitrosamine; TSNA = tobacco-specific *N*-nitrosamine

Despite the ubiquity of PAHs in modern society, their presence in and their contribution to the alleged hazard of tobacco smoke have been repeatedly emphasized. The anti-tobacco smoking force seldom acknowledges that many sources of PAHs exist. Daily exposure to these compounds by inhalation (main-stream cigarette smoke, environmental tobacco smoke, air pollutants) may represent only a small part of the total daily exposure; other exposures to PAHs often substantially exceed exposure via inhalation.

The results from numerous studies have been reported on the determination of the types and levels of PAHs, with particular emphasis on the levels of BaP as well as BaA, chrysene, benz[*e*]acephenanthrylene(benzo[*b*]fluoranthene),benzo[*k*]fluoranthene,indeno[1,2,3-*cd*]pyrene, DBA, and benzo[*ghi*]perylene. As noted by Menzie *et al.* (1992), these have been identified in exhausts or effluents from fossil fuel combustion sources, in soils, sediments, and water, and in a variety of commonly used foodstuffs. **Tables 7 and 8** summarizes in slightly different ways some of the PAH findings from other sources. Although concern about PAHs in foodstuffs, particularly those arising pyrogenetically during cooking (grilling, broiling, roasting, etc.) predates the major concern of their presence in tobacco smoke, the efforts to identify them in foodstuffs have been much less than the tobacco smoke effort: As noted previously, the number of PAHs unequivocally identified in tobacco smoke exceeds 500. In addition, several hundred derivatives where the positions of the alkyl groups have not been precisely defined have been partially identified. PAHs identified in foodstuffs, both cooked and uncooked, number fewer than 150. Whether one considers the overall composition in general or the PAH fraction in particular, no other commercial product has been examined as extensively as tobacco smoke.

TABLE 7: PERSONAL EXPOSURE TO TOBACCO SMOKE COMPONENTS LISTED AS TUMORIGENIC BY HOFFMANN AND HECHT (1990) AND CARCINOGENIC BY OSHA (1994)

Exposure Source	BaA[abc]	BbF[ab]	BjF[a]	BkF[ab]	BaP[ab]	Chr[a]	Chr, Me[ab]	DBA[ab]	DBeP[b]	DBhP[b]	DBiP[ab]	DBlP[ab]	IP[ab]
Fish													
raw	✓	✓		✓	✓								
cooked	✓	✓		✓	✓								
smoked					✓								
Oysters	✓				✓								
Mussels					✓								
Meat													
frankfurters					✓								
hamburgers	✓	✓		✓	✓			✓	✓	✓			✓
bacon					✓								
ham, smoked					✓								
bologna					✓								
sausage	✓				✓								
beef, broiled	✓				✓								
beef, roasted	✓				✓								
beef, barbecued					✓								
poultry					✓								
cholesterol, heated						✓							
Dairy products													
milk					✓								
cheese					✓								
Cereals													
puffed corn		✓		✓	✓								
puffed oats	✓	✓											
puffed wheat		✓		✓	✓								
barley malt	✓	✓			✓			✓					✓
bran	✓	✓		✓	✓								
Bread													
untoasted					✓								
toasted					✓								
Beverages													
tea					✓								
coffee, regular					✓								
coffee, instant					✓								
water		✓			✓								
bourbon					✓								✓
scotch					✓								
Fruits and Vegetables													
fresh	✓				✓								
potatoes, cooked					✓								
potatoes, French fried					✓								
endive					✓								
spinach					✓								
soybeans					✓								
kale					✓								
tomatoes					✓								
apples					✓								
prunes					✓								
Oils, cooking													
coconut oil	✓				✓								
vegetable oils	✓				✓								
Mayonnaise	✓				✓								
Margarine	✓				✓								

Table 7: Continued

Exposure Source	BaA[a,b,c]	BbF[a,b]	BjF[a]	BkF[a,b]	BaP[a,b]	Chr[a]	Chr, Me[a,b]	DBA[a,b]	DBeP[a,b]	DBhP[a,b]	DBiP[a,b]	DBlP[a,b]	IP[a,b]
Environmental tobacco smoke[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Diesel/gasoline engine exhausts[c,f,g]	✓	✓	✓	✓	✓	✓	✓	✓					✓
Industry-related tars, soots, oils, etc. (excluding ETS)[f]	✓	✓		✓	✓	✓		✓					✓
Oils, catalytically cracked	✓				✓	✓	✓						
Carbon blacks used in truck and automobile tires	✓				✓	✓							
Open-fire, coal combustion[h]	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓
Urban atmospheres	✓				✓	✓	✓						

[a] Listed in Hoffmann and Hecht (1990)
[b] Listed in Table II-2 (OSHA, 1994)
[c] BaA = benz[*a*]anthracene BbF = benzo[*b*]fluoranthene BjF = benzo[*j*]fluoranthene BkF = benzo[*k*]fluoranthene BaP = benzo[*a*]pyrene Chr = chrysene Chr,Me = chrysene, 5-methyl- DBA = dibenz[*a,h*]anthracene DBeP = dibenzo[*a,e*]pyrene (naphtho[1,2,3,4-*def*]chrysene) DBhP = dibenzo[*a,h*]pyrene (dibenzo[*b,def*]chrysene DBiP = dibenzo[*a,i*]pyrene (benzo[*rst*]pentaphene DBlP = dibenzo[*a,l*]pyrene (dibenzo[*def,p*]chrysene: see discussion Table 4)
IP = indeno[1,2,3-*cd*]pyrene]
[d] The polycyclic aromatic hydrocarbons listed also occur in MS and SS
[e] Wynder and Hoffmann (1962a)
[f] Williams *et al.* (1986)
[g] Grimmer *et al.* (1991)
[h] Mumford *et al.* (1987)

Many PAHs are components of foodstuffs in the average diet. Except for 5-methylchrysene, PAHs listed by Hoffmann and Hecht (1990) and OSHA (1994) as tobacco and tobacco smoke "tumorigens" have been identified in many foodstuffs. Grasso (1984) discussed the PAHs in foods and their significance as follows:

> The significance of these low levels of [polycyclic aromatic hydrocarbon] carcinogens in food is difficult to assess. Undoubtedly, they are among the most potent carcinogens known, and every effort should be made to reduce their concentration in food. There are no clear indications, however, that they cause human cancer... Furthermore, there are indications that low levels of [benzo[*a*]pyrene], probably one of the most potent of the [polycyclic aromatic hydrocarbons] found in food, do not produce tumors in experimental animals. The repeated application of 1.25 μg of [benzo[*a*]pyrene] in acetone to the skin of mice for 68 weeks failed to produce tumors (Roe, [1962, 1963]; dietary intake of 100 ppm of [benzo[*a*]pyrene] or less also had no effect in mice [Neal and Rigdon, 1967].

His comments on the carcinogenicity of PAHs in foods to humans are equally applicable to the carcinogenicity to humans of the PAHs in inhaled MS or ETS.

TABLE 8: POLYCYCLIC AROMATIC HYDROCARBON SOURCES

Polycyclic Aromatic Hydrocarbons	Tobacco Smoke	Gasoline Engine Exhaust[a]	Cooked Fish[b]	Broiled Hamburger[b]	Barley Malt[bh]	Puffed Cereals[b]	Common Foods[b]
benz[*j*]aceanthrylene, 1,2-dihydro-[c]	✓						✓
benz[*j*]aceanthrylene, 1,2-dihydro-3-methyl-[d]	✓						✓
benz[*e*]acephenanthrylene[e]	✓		✓	✓		✓	✓
benz[*a*]anthracene	✓	✓	✓	✓	✓	✓	✓
benz[*a*]anthracene, 7,12-dimethyl-	✓			✓		✓	✓
benzo[*j*]fluoranthene	✓	✓					✓
benzo[*k*]fluoranthene	✓	✓	✓	✓		✓	✓
11*H*-benzo[*b*]fluorene	✓	✓					✓
benzo[*rst*]pentaphene[f]	✓						✓
benzo[*ghi*]perylene	✓	✓	✓				✓
benzo[*c*]phenanthrene	✓						✓
benzo[*a*]pyrene	✓	✓	✓		✓	✓	✓
benzo[*e*]pyrene	✓	✓	✓				✓
benzo[*b*]triphenylene[g]	✓			✓	✓		✓
chrysene	✓	✓		✓			✓
dibenz[*a,h*]anthracene	✓	✓		✓	✓		✓
dibenz[*a,j*]anthracene	✓	✓					✓
dibenzo[*e,l*]pyrene[i]	✓			✓			✓
indeno[1,2,3-*cd*]fluoranthene	✓	✓					✓
indeno[1,2,3-*cd*]pyrene	✓	✓					✓

[a] Wynder and Hoffmann (1962a)
[b] Maga (1988)
[c] Previously known as cholanthrene
[d] Previously known as 3-methylcholanthrene
[e] Previously known as benzo[*b*]fluoranthene
[f] Previously known as dibenzo[*a,l*]pyrene
[g] Previously known as dibenz[*a,c*]anthracene
[h] Also contains a high level of *N*-nitrosodimethylamine
[i] Also known as dibenzo[*fg,op*]naphthacene

Grasso noted that five PAHs were commonly found in foods: BaA, BaP, DBA, benz[*e*]acephenanthrylene (benzo[*b*]-fluoranthene), and benzo[*k*]fluoranthene; all listed by Hoffmann and Hecht and OSHA as "tobacco smoke tumorigens." In **Table 9** is a list compiled by Grasso of the ranges of the BaP and BaA levels found in a variety of commonly consumed foodstuffs.

More recently, Maga (1988) listed 65 common PAHs-containing foodstuffs. These, as did the list compiled by Grasso (**Table 9**), included fruits and vegetables, dairy products, cereal

products, legumes, beverages (including water), cooking oils, meat products, seafood products, and miscellaneous foodstuffs such as eggs, sugar, and olives. When many foodstuffs are heated during preparation, their PAH content increased dramatically, *e.g.*, a single serving of charcoal-broiled meat contains more than 600 times the BaP level in the MS from one cigarette (Lijinsky and Shubik, 1964, 1965). Estimates such as this one are usually based on the Federal Trade Commission's (FTC) listing of TPM, "tar," nicotine, and carbon monoxide deliveries plus an average value for the level of the BaP in the MS TPM. Such comparisons between cigarettes and foodstuffs may yield estimates that are actually too low. For a given cigarette brand, the FTC numbers are obtained via a precisely defined smoking regime and analytical methods [preconditioned cigarettes (25°C; relative humidity, 60%; conditioning time, 24 hr); smoking parameters — 35-ml puff volume, 2-sec puff duration, 1 puff/min; 25°C, 60% relative humidity, cigarette smoked to a defined butt length]. On the other hand:

- Few smokers, if any, in the smoking of a cigarette take in the TPM amount found in the FTC determination.
- Few smokers smoke their cigarettes to as short a butt length as in the FTC procedure.
- Because of involvement in other tasks, the smokers often place their cigarette in an ash tray for a brief time, thus missing one or more puffs on the cigarette. Few smokers take the number of puffs obtained for a given cigarette brand in the FTC procedure. The smoking machine used in the FTC period never misses a puff on the cigarette under test!
- The smoking machine used in the FTC procedure does not "exhale" as do smokers. It has been determined in numerous studies that cigarette smokers exhale between 10 and 50% of the TPM inspired during the puffs needed to consume the cigarette, thus retaining between 50% and 90% of the inspired TPM.

All of these factors, if taken into account for a foodstuff-cigarette comparison such as the one noted previously, will increase the calculated number of cigarettes in the BaP comparison.

Analysis of a foodstuff as elementary as bread reveals a BaP level of 0.23 ng/g (mainly in the crust); light toasting raised the level to 0.39 ng/g; darker toasting raised it to 0.56 ng/g. For an average slice of bread, weight one ounce (approximately 30 g), these values would be about 7, 12, and 17 ng/slice. Maga also reported the dietary intake of BaP (charcoal-broiled meat excluded) averaged about 500 ng/day. From their analysis of human exposure to BaP, Waldman *et al.* (1991) reported that "the range and magnitude of dietary exposures" ranged from 2 to 500 ng/day and "were much greater than for inhalation (10 to 50 ng/[day])." For some subjects, however, they found a dietary maximum of 1149 ng/day, despite omission of the contribution of BaP-containing beverages. These BaP-intake estimates (Maga; Waldman *et al.*) were lower than that reported by Hattemeyer-Frey and Travis (1991): 2,200 ng/day (97% from diet; 3% from inhalation and water contamination). If BaP were tumorigenic in man and its threshold limit value were "zero," the incidence of digestive tract cancer would be substantially higher than it is.

TABLE 9: LEVELS OF BENZO[*a*]PYRENE AND BENZ[*a*]ANTHRACENE IN COMMON FOODSTUFFS

Foodstuff	Benzo[*a*]pyrene, ng/g	Benz[*a*]anthracene, ng/g
Fresh vegetables	2.85-24.5	0.3-43.6
Vegetable oils	0.4-1.4	0.8-1.1
Coconut oil	43.7	98.0
Margarine	0.4-0.5	1.4-3.0
Mayonnaise	0.4	2.2
Coffee	0.3-1.3	1.3-3.0
Tea	3.9	2.9-4.6
Grain	0.19-4.13	0.40-6.85
Oysters and mussels	1.5-9.0	...
Smoked ham	3.2	2.8
Smoked fish	0.83	1.9
Smoked bonito	37	189
Cooked sausage	12.5-18.8	17.5-26.2
Singed meat	35-99	28-79
Broiled meat	0.17-0.63	0.2-0.4
Charcoal-broiled steak	8.0	4.5
Broiled mackerel	0.9	2.9
Barbecued beef	3.3	13.2
Barbecued ribs	10.5	3.6
Cigarette MS[a]	20-25	20-35

[a] The total MS (particulate phase plus vapor phase) from an 85-mm filtered cigarette smoked under FTC conditions approximates 0.5 g.

How do these exposures to BaP in the diet, etc. compare to the exposure to BaP in ETS? It is obvious that dietary intake of BaP far outweighs the intake of BaP via inhalation, including that inhaled in ETS. Guerin *et al.* (1992) discussed the contribution of ETS to indoor air PAH concentrations and tabulated their assessments of the situation. They noted:

> The data suggest that ETS contributes between 0.5 and 1 ng/m^3 of BaP to indoor environments containing measurable ETS-contamination... Excursions in BaP concentrations due to ETS in such environments reach approximately 2.5 ng/m^3... The magnitude of ETS-contribution [to PAH and BaP concentration] is generally small and is often difficult to consistently detect in most environments.

The daily intake of BaP from ETS may be estimated if the following assumptions are made:

- The average hourly intake of air is independent of whether the host is awake or asleep and is 1 m^3.
- The BaP level due ETS to is at the high end of the range estimated by Guerin *et al.* (1992) to be 0.5 to 1 ng/m^3.
- None of the daily intake of BaP, whether from diet, ETS, and the like, is eliminated by exhalation, etc.

The following shows a comparison of the intake of BaP from ETS *vs* the other BaP intakes discussed previously:

Study	Type	BaP from Diet	BaP via Inhalation	Total BaP Intake
Maga (1988)	Estimated			500 ng/day
Hattemeyer-Frey and Travis (1991)	Measured	2,130 ng/day	70 ng/day	2,200 ng/day
Waldman *et al.* (1991)	Measured	2-500 ng/day[a]	10-50 ng/day	12-550 ng/day[a]
From inhaled ETS	Estimated		24 ng/day	

[a] Dietary intakes as high as 1,149 ng/day were noted.
[b] Based on assumptions listed above
[c] Even if intake were at the excursion value of 2.5 ng/m^3, the daily intake from ETS would 60 ng

Holcomb (1993) reviewed the studies which attempted to actually calculate the impact that ETS had on indoor air quality and the ETS doses one might receive from possible exposures in several different settings. Holcomb, aware of the differences among the chemical and physical properties of MS, SS, and ETS, noted:

> The mainstream smoke particles inhaled during the act of puffing on a cigarette will be quite different from ETS particles in terms of their precise chemical composition, their size distribution and the route in which they are taken into the body.

The latter comment relates to the fact that cigarette MS is inhaled orally whereas ETS is usually inhaled nasally. Holcomb also pointed out a misinterpretation often repeated by various persons and agencies, *e.g.*, the U.S. Surgeon General, EPA, and more recently OSHA (1994), subsequent to Holcomb's publication. Holcomb also noted:

> The U.S. Surgeon General [USPHS, 1987] and NRC [NAS, 1986] reports include summary tables of known or suspect human carcinogens present in concentrated sidestream and mainstream tobacco smoke. Concentrated sidestream and mainstream tobacco smoke are not representative of ambient air ETS because the concentrated smoke is subject to dilution in ambient air, removal by sinks or filtration, and possible transformation [Reasor, 1987].

In contrast to the relatively simple set of assumptions used to compare exposure to PAHs in ETS with that from dietary components, Holcomb — with data from Rosenblatt *et al.* (1982), the EPA (1989), Arundel *et al.*, (1988), and Hiller *et al.* (1982a, 1982b, 1987) — used the

following values for respiration rate, % retention of ETS (and SS) particles, and retention of MS on direct cigarette smoking:

male, awake	1.05 m^3/hr	25.2 m^3/d
male, asleep	0.4 m^3/hr	9.6 m^3/d
female, awake	0.65 m^3/hr	15.6 m^3/d
female, asleep	0.3 m^3/hr	7.2 m^3/d
male, % retention, direct smoking		10.56 mg/cigt
female, % retention, direct smoking		8.48 mg/cigt
retention, %		11

After elaborate calculations, Holcomb commented on respiratory exposure via ETS to several compounds and classes of compounds on the two "Lists of 43" (Table 4): PAHs, NNAs, formaldehyde, benzene, and aza-arenes[d]. His apportioning different respiration rates to different periods of the day and his use of 11% retention will substantially lower the estimated exposure to BaP *vs* my use of 1 ng/m^3/hr respiration rate and 100% retention. If the more recent data of McAughey *et al.* (1994) for the % retention of particulates from *aged and diluted SS* be used in the calculations (17 to 41%, depending on analytical procedure and subjects' gender), the estimated exposure obviously will not be lowered as much as when the 11% retention from the Hiller *et al.* study is used.

On exposure to PAHs in ETS, Holcomb wrote:

> PAHs are commonly found in indoor air. Except for naphthalene, quinoline[d] [*sic*], and isoquinoline[d] [*sic*], the levels measured are in the low ng/m^3 range... Few studies have compared PAH levels in smoking and nonsmoking environments. The two studies in this review...indicate that between 50% and 80% of the concentration of various PAHs may come from tobacco smoke. Because of the paucity of data, this must be interpreted with caution. The presence of these substances has also been documented in wood smoke, automobile exhaust, foods, alcoholic beverages, and cosmetics...

Holcomb concluded:

> Until the problems of confounding and bias in the epidemiology studies are resolved, dosimetric considerations can be the only independent confirmation of the accuracy of their claims. *At this point, it can be only concluded that the estimated dose of ETS one can be expected to receive does not support the health risk claims made by* [the U.S. EPA (EPA, 1990)] *and others. (Emphasis added:* AR)

For some years, considerable research has been involved in attempts to determine whether the PAHs that induce tumors in laboratory animals by a variety of administration routes are tumorigenic *per se* or tumorigenic via one or more of their metabolic products, the variety

[d] In his discussion of PAHs and NNAs, Holcomb classified the two aza-arenes quinoline and isoquinoline as PAHs.

of dihydrodiol epoxides formed. In their excellent review on the chemical carcinogenicity of PAHs, Dipple *et al.* (1984) summarized the situation at that time:

> Over the years, a direct mechanism of action for the hydrocarbon carcinogens, in which metabolism serves only a detoxification role, and an indirect mechanism of action, wherein a metabolite of the hydrocarbon is responsible for the initiation of carcinogenesis, have both been advocated strongly at various times. It was possible to support both these mutually exclusive hypotheses and a number of different ideas, in the case of the indirect mechanism, about which particular metabolite(s) might be responsible for carcinogenic activity, because there was a complete lack of any critical evidence which could exclude one possibility or another. In the last few years, the situation changed considerably, and it is becoming increasingly clear that the carcinogenic action of the hydrocarbons is probably expressed through metabolites associated with the dihydrodiol epoxide pathway.

Failure to generate the tumorigenic isomer of the PAH dihydrodiol epoxides or generation of low levels of the tumorigenic isomer of the PAH dihydrodiol epoxides *vs* other nontumorigenic isomers has been offered as the explanation for the difference in tumorigenicities observed in different laboratory animal species treated with PAHs such as BaP, *e.g.*, mouse *vs* rabbit where the rabbit is much more resistant to tumor production (Berenblum and Schoental, 1947; Wynder, Fritz, and Furth, 1957) or mouse *vs* primate (Hartwell, 1951; Shubik and Hartwell, 1957, 1969) where the primate is refractory to tumor induction by PAHs.

PAHs in tobacco smoke, particularly those classified as "tumorigens" because they are reported to induce tumors in mouse skin-painting experiments as well as those nontumorigenic PAHs reported to influence tumorigenicity because of their promoting or cocarcinogenic properties, have been discussed at length in numerous reports such as various Surgeon Generals' reports (USPHS, 1964, 1979, 1981), IARC monographs (IARC, 1986), and review articles by investigators such as Hoffmann and Hecht (1990). **Table 10** summarizes which PAHs were discussed in several of these key publications.

It is interesting to note, however, the complete absence of any discussion of carcinogenic PAHs in tobacco smoke in the two-volume 1984 edition of the American Chemical Society monograph on chemical carcinogens (Searle, 1984). The only "tobacco smoke tumorigens" discussed in the monograph are the NNAs (which play little or no part in the results obtained in skin-painting bioassays with CSC). In their contribution to the monograph, Dipple *et al.* (1984) classified the carcinogenic activity of several of the PAHs differently from those who were discussing their presence in tobacco smoke, *cf.* Hoffmann and Hecht (1990), the 1979, 1981, and 1982 Surgeon General (USPHS, 1979, 1981, 1982). *E.g.*, Dipple *et al.* classified the carcinogenic activities of chrysene, BaA, and benzo[*b*]triphenylene (dibenz[*a,c*]anthracene) as "disputed." They classified dibenzo[*def,mno*]chrysene (anthanthrene) and benzo[*e*]pyrene as "inactive."

The discussion in the IARC monograph (1986) of the PAHs in tobacco smoke involved a much greater number (41) of PAHs than did the other reports cited in **Table 10**. However, the IARC, using objective criteria, characterized the degree of evidence for carcinogenicity either in animals or man of many of them as follows:

Evidence for Carcinogenicity Characterized by IARC as

"None"	"Inadequate"		"Limited"
anthracene	benzo[*ghi*]fluoranthene	coronene	benzo[*b*]triphenylene
fluoranthene	benzo[*a*]fluorene	fluoranthene, 3-methyl-	chrysene[a]
pyrene	benzo[*b*]fluorene	fluorene	chrysene, 2-methyl-
	benzo[*c*]fluorene	perylene	chrysene, 3-methyl-
	benzo[*ghi*]perylene	phenanthrene	chrysene, 4-methyl-
	benzo[*c*]phenanthrene	phenanthrene, 1,4-dimethyl-	chrysene, 6-methyl-
	benzo[*e*]pyrene	phenanthrene, 1-methyl-	dibenz[*a,e*]aceanthrylene[bc]
	chrysene, 1-methyl-	triphenylene	dibenz[*a,j*]anthracene
			dibenzo[*def,mno*]chrysene
			fluoranthene, 2-methyl-

[a] Listed as a tobacco smoke "tumorigen" by Hoffmann and Hecht (1990)
[b] Listed as a tobacco smoke "tumorigen" by Hoffmann and Hecht (1990) and by OSHA (1994)
[c] Structure of tobacco smoke PAH originally thought to be dibenzo[*a,l*]pyrene

TABLE 10: POLYCYCLIC AROMATIC HYDROCARBONS DISCUSSED IN VARIOUS REPORTS AND MONOGRAPHS

Polycyclic Aromatic Hydrocarbon	USPHS, 1964[a]	USPHS, 1979	USPHS, 1981, 1982	IARC, 1986	OSHA, 1994[b]	Hoffmann & Hecht, 1990[c]
• *Listed as "Tumorigenic"*						
benz[*e*]acephenanthrylene {benzo[*b*]fluoranthene}		✓	✓	✓	✓	✓
benz[*a*]anthracene		✓	✓	✓	✓	✓
benzo[*j*]fluoranthene	✓	✓	✓	✓		✓
benzo[*k*]fluoranthene				✓	✓	✓
benzo[*a*]fluorene[d]				✓		
benzo[*b*]fluorene[e]				✓		
benzo[*c*]fluorene[f]				✓		
benzo[*rst*]pentaphene {dibenzo[*a,i*]pyrene}	✓	✓[g]	✓	✓	✓	✓
benzo[*c*]phenanthrene	✓	✓	✓	✓		
benzo[*a*]pyrene	✓	✓	✓	✓	✓	✓
benzo[*e*]pyrene		✓	✓	✓		
benzo[*b*]triphenylene {dibenz[*a,c*]anthracene}		✓	✓	✓		
chrysene		✓	✓	✓		✓
chrysene, 1-methyl-		✓	✓	✓		
chrysene, 2-methyl-		✓	✓	✓		
chrysene, 3-methyl-		✓	✓	✓		
chrysene, 4-methyl-				✓		
chrysene, 5-methyl-		✓	✓	✓	✓	✓
chrysene, 6-methyl-		✓	✓	✓		
coronene				✓		
dibenz[*a,e*]aceanthrylene {dibenzo[*a,e*]fluoranthene}[h]				✓		

Table 10: Continued

Polycyclic Aromatic Hydrocarbon	USPHS, 1964[a]	USPHS, 1979	USPHS, 1981, 1982	IARC, 1986	OSHA, 1994[b]	Hoffmann & Hecht, 1990[c]
• *Listed as "Tumorigenic" (cont.)*						
dibenz[*a,h*]anthracene	✓	✓	✓	✓	✓	✓
dibenzo[*a,j*]anthracene				✓		
dibenzo[*b,def*]chrysene {dibenzo[*a,k*]pyrene}		✓	✓	✓	✓	
dibenzo[*def,mno*]chrysene {anthanthrene}				✓		
dibenzo[*def,p*]chrysene {dibenzo[*a,l*]pyrene}[b]	✓			✓	✓	✓
fluoranthene, 2-methyl-		✓	✓	✓		
fluoranthene, 3-methyl-		✓	✓	✓		
indeno[1,2,3-*cd*]pyrene		✓	✓	✓	✓	✓
naphtho[1,2,3,4-*def*]chrysene {dibenzo[*a,e*]pyrene}				✓	✓	
• *Listed as Nontumorigenic and/or Promoting/Cocarcinogenic*						
acenaphthene	✓					
acenaphthylene	✓					
anthracene	✓			✓		
benzo[*ghi*]perylene		✓	✓	✓		
benzo[*e*]pyrene			✓	✓		
fluoranthene		✓	✓	✓		
fluoranthene, methyl-			✓			
fluorene	✓			✓		
naphthalene			✓			
perylene				✓		
phenanthrene	✓			✓		
phenanthrene, 1,4-dimethyl-				✓		
phenanthrene, 1-methyl-				✓		

Table 10: Continued

Polycyclic Aromatic Hydrocarbon	USPHS, 1964[a]	USPHS, 1979	USPHS, 1981, 1982	IARC, 1986	OSHA, 1994[b]	Hoffmann & Hecht, 1990[c]
• *Listed as Nontumorigenic and/or Promoting/Cocarcinogenic (cont.)*						
pyrene	✓	✓	✓	✓		
pyrene, methyl-		✓	✓			
triphenylene				✓		

[a] It was noted that 27 PAHs had been identified in tobacco smoke by the time of publication of this report; only the 12 noted were discussed specifically.
[c] OSHA (1994) listed the PAHs indicated as tobacco smoke components for which there is "sufficient evidence" of carcinogenicity in humans or animals.
[c] Hoffmann and Hecht (1990) listed the PAHs indicated as "*Tumorigenic Agents in Tobacco and Tobacco Smoke.*"
[d] Authors did not indicate whether isomer under discussion was the 5*H*- or the 11*H*-benzo[*a*]fluorene.
[e] Authors did not indicate whether isomer under discussion was the 5*H*- or the 11*H*-benzo[*b*]fluorene.
[f] Authors did not indicate whether isomer under discussion was the 7*H*- or the 11*H*-benzo[*c*]fluorene.
[g] Listed incorrectly as dibenzo[*a,j*]pyrene.
[h] The first reported identification of dibenzo[*a,l*]pyrene (dibenzo[*def,p*]chrysene) in tobacco smoke was based on spectral properties of a synthetic PAH thought to be dibenzo[*a,l*]pyrene. Subsequently the synthetic was shown to be dibenzo[*a,e*]fluoranthene (dibenz[*a,e*]acenanthrylene) (Lavit-Lamy and Buu-Hoï, 1966). Later, a bonafide identification of dibenzo[*a,l*]pyrene (dibenzo[*def,p*]chrysene) in tobacco smoke was reported (Snook *et al.*, 1977).
[i] Also listed above as a tumorigen.

During the almost two decades between the 1964 and the 1982 Surgeon Generals' smoking-and-health reports, the components (PAHs and their heterocyclic analogs) reported to be involved in the mouse-skin carcinogenesis observed with tobacco smoke were studied intensively. Despite the enormous expenditure of money, time, and effort in studying these components, there is very little difference in the statements on the PAHs in these two reports or the 1979 report: The observed tumorigenicity to mouse skin of CSC cannot be explained by its levels of tumorigenic PAHs [or by the levels of any other class of allegedly biologically active components (promoters, cocarcinogens) acting individually or in concert]. Examination of the sequence of statements (**Table 11**) from several Surgeon Generals' reports on the tumorigenic PAHs indicates that little had changed. In the interim, the "indicator" or "marker" concepts as applied to BaP and phenol in tobacco smoke were vigorously promoted, but already existing and newly generated laboratory data eventually showed the concepts were incorrect. This was recognized in the 1981 Surgeon General's report (**Table 11**).

In summary, the situation with regard to the "tumorigenic" PAHs in MS considered to be significant in ETS by OSHA and EPA is as follows:

TABLE 11: SURGEON GENERALS' VIEWS ON POLYCYCLIC AROMATIC HYDROCARBONS IN TOBACCO SMOKE

1964 Surgeon General's Report (USPHS, 1964)	1979 Surgeon General's Report (USPHS, 1979)	1981 Surgeon General's Report (USPHS, 1981)	1982 Surgeon General's Report (USPHS, 1982)
At page 58: "The results of a number of such assays [mouse skin-painting] present a puzzling anomaly: the total tar from cigarettes has about 40 times the carcinogenic potency of the benzo(a)pyrene [*sic*] present in the tar.The other carcinogens known to be present in tobacco smoke are, with the exception of dibenzo-(a,i)pyrene [*sic*], much less potent than benzo-(a)pyrene and they are present in smaller amounts. **Apparently, therefore, the whole is greater than the sum of the known parts** (Kennaway and Lindsey, 1958; Orris *et al.*, 1958; Wynder *et al.*, 1957)." *At page 144-145:* "Benzo(a)pyrene [*sic*] is present in much larger concentrations than is any other carcinogenic polycyclic hydrocarbon. The inability to account for the carcinogenicity of the tobacco products, except to a very minor degree, by the amount of	*At page 14-51:* "PAH alone, however, account for only a small portion of the carcinogenicity of tobacco 'tar'... **The levels of carcinogenic PAH in tobacco smoke are well below their practical threshold as complete mouse skin carcinogens...**" *At page 14-109/111:* "Since the mechanism of the pyrosynthesis of PAH from C,H- [*sic*] radicals is valid for most of the PAH in tobacco smoke, benzo(a)pyrene [*sic*] is often used generally as an **indicator of PAH levels** and specifically as an **indicator of carcinogenic potential of the smoke as measured in animal experiments.** However, this 'indicator' concept can be applied only to smoke deriving from cigarettes primarily made up of the same precursor material, *i.e.*, tobacco leaves. The 'indicator' concept was applied in measuring BaP formation in many attempts to achieve PAH reduction in smoke."	*At page 36:* "Of the PAHs, benzo-[*a*]pyrene (BaP) is the most prominent and has been studied most intensively. Chemical assays for BaP in smoke condensates are well established, and it has been suggested that such assays can serve as indicators of production of all the PAHs. This appears to be generally true. Among smoke condensates from 98 experimental cigarettes, the correlation coefficient between BaP and benz[*a*]anthracene was 0.78... Although highly significant, **the value is sufficiently low to indicate that real differences do exist in the ratios of these cyclic molecules in the various cigarette smokes...** "The contribution of BaP or PAH in general to mouse skin carcinogenesis by cigarette smoke condensate cannot be fully measured at this time. Wynder and Hoffmann [1967] found a correlation between BaP levels and carcinogenicity of smoke	*At page 195:* "**The carcinogenic activity of the particulate matter of tobacco smoke in epithelial tissues of laboratory animals is greater than the sum of the effects of the known carcinogens present.**" This statement in the report is immediately followed by a totally incorrect statement: "Large scale fractionation studies in a number of laboratories have shown that the total carcinogenic activity also results from the effects of tumor initiators, tumor promoters, and cocarcinogens in the tar." An explanation of the total carcinogenicity of MS particulate matter, CSC, or "tar" on the basis of their content of initiators, promoters, and cocarcinogens has *never* been accomplished either experimentally in the laboratory or by calculation.

Table 11: Continued

1964 Surgeon General's Report (USPHS, 1964)	1979 Surgeon General's Report (USPHS, 1979)	1981 Surgeon General's Report (USPHS, 1981)	1982 Surgeon General's Report (USPHS, 1982)
benzo(a)pyrene present was unanticipated. **Both Druckrey (1961) and Wynder (1961) emphasized that the benzo(a)pyrene concentration of various tobacco and smoke preparations is only sufficient to account for a very small part of the carcinogenicity of these materials."**		condensates from several types of cigarettes. A much larger series of experimental cigarettes was studied in the smoking and health program of the National Cancer Institute. **No significant dependence of carcinogenic potency on BaP content was observed** [Gori, 1976a, 1976b, 1977, 1980]."	
		At page 93-94:	
NOTE:		"Extensive fractionation studies combined with bioassays have supported the concept that **the concentration in cigarette 'tar' of certain polynuclear aromatic hydrocarbons (PAH)... is too low to account for their activity as complete carcinogens."**	
Even though BaA had been identified in tobacco smoke by several investigators prior to 1964, it was not listed as a carcinogenic PAH in the 1964 report. In most pre-1960 carcinogenicity studies (mouse skin-painting) with BaA, it was found to be noncarcinogenic or very weakly carcinogenic compared to BaP or DBA.	*At page 14-54:* In this report, BaA is listed as a weak carcinogen to mouse skin.	*At page 34:* In this report, BaA is listed as a tumor initiator.	

[a] At least as recently as 1979, the U. S. Surgeon General admitted that there was indeed a threshold for tumorigenicity.

NOTE: **Highlighted material, emphasis added.**

- There is lack of unanimity on the tumorigenicity of several of the PAHs listed, *e.g.*, BaA, chrysene.

- The per cigarette levels and tumorigenic potency of several of the PAHs in tobacco smoke are insignificant *vs* those of BaP, *e.g.*, benzo[*b*]fluoranthene (benz[*e*]-acephenanthrylene), benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, 5-methylchrysene.

- The identity of one of the PAHs as listed, dibenzo[*a,l*]pyrene (dibenzo[*def,p*]-chrysene), is doubtful. In addition, no quantitative data are provided for the PAH listed as dibenzo[*a,l*]pyrene.

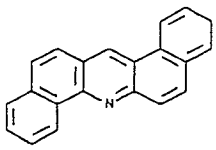
- None of the PAHs listed has produced squamous cell carcinoma in laboratory animals exposed to the PAH at reasonable concentrations via inhalation. Even the tumorigenicity of BaP under these exposure conditions has been questioned.

- The levels of several of the PAHs listed are those obtained for cigarette manufactured prior to 1973 and therefore are not pertinent to more recently manufactured cigarettes.

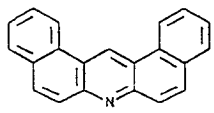
- The levels of several PAHs listed are those reported not only from a single laboratory but also on pre-1973 cigarettes, *e.g.*, 5-methylchrysene, DBA, dibenzo[*a,l*]pyrene (dibenzo[*def,p*]chrysene).

Aza-arenes

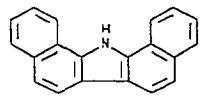
Within a few years of the discovery of the tumorigenicity to mouse skin of the PAHs DBA (Kennaway and Hieger, 1930) and BaP (Cook *et al.*, 1932, 1933), investigations on the tumorigenicity of aza-arenes began. The aza-arenes selected for study were those structurally related to the PAHs already demonstrated to be tumorigenic. The first aza-arenes studied were those corresponding to dibenzanthracenes in which one *meso-carbon* was replaced by a nitrogen atom. From a comparison of their tumorigenicities (mouse skin-painting experiments), Barry *et al.* (1935) reported that the tumorigenicity of several dibenzacridines was much less than the corresponding PAH, *e.g.*, dibenz[*a,h*]acridine (I) was reported to be much less tumorigenic than DBA (IV) under the same experimental conditions.



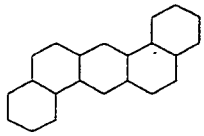
dibenz[*a,h*]acridine, I



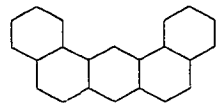
dibenz[*a,j*]acridine, II



7*H*-dibenzo[*c,g*]carbazole, III



dibenz[*a,h*]anthracene, IV



dibenz[*a,j*]anthracene, V

For the PAHs, much of the early research on their synthesis and tumorigenicity was conducted by Kennaway's group (Barry, Cook, Hieger, Lindsey, Schoental, etc.) in the U.K., by groups headed by Fieser and Newman in the U.S.A., and by Clar's group in Germany. For the aza-arenes such as the benzacridines, much of the early work was conducted by Lacassagne's group (Buu-Hoï, Daudel, Lavit-Lamy, Zajdela, etc.) in France.

Examination of the results of tobacco smoke isolation studies and their tumorigenic properties leads one to conclude that inclusion in both "Lists of 43" of the three aza-arenes dibenz[*a,h*]acridine (I), dibenz[*a,j*]acridine (II), and 7*H*-dibenzo[*c,g*]carbazole (III) as presumably significant tumorigens may be more political than scientific.

It has been known for nearly six decades (*cf.* review by Lacassagne *et al.*, 1956) from the comparative tumorigenicity studies involving structurally similar PAHs and aza-arenes that the aza-arenes are much less tumorigenic than the PAHs to mouse skin [*cf.* DBA (IV) *vs* dibenz[*a,h*]acridine (I) and dibenz[*a,j*]anthracene (V) *vs* dibenz[*a,j*]acridine (II) or 7*H*-dibenzo[*c,g*]carbazole (III)]. These observations on tumorigenicity plus the reported amounts of the three aza-arenes in cigarette MS relative to the amount of BaP certainly raises doubts as to the importance of the aza-arenes as significant tobacco smoke tumorigens. From the "Lists of 43" and **Table 4**, BaP is listed as occurring in cigarette MS in amounts ranging from 20 to 40 ng/cigt whereas the per cigarette deliveries of the aza-arenes I, II, and III are listed at 0.1, 3-10, and 0.7 ng/cigt, respectively. Even though a more realistic range for BaP in the MS of cigarettes marketed over the past two decades would be 5 to 20 ng/cigt rather than 20 to 40 ng/cigt, the ratios of BaP delivery to those of dibenz[*a,h*]acridine and 7*H*-dibenzo[*c,g*]carbazole are substantial. This of course assumes that the delivery levels for the three aza-arenes that were included in the "Lists of 43" are correct! It is obvious that the listed aza-arene delivery levels are not meaningful for recently manufactured cigarettes whose design includes technologies not used in the late 1950s and early 1960s when Van Duuren *et al.* (1960a, 1960b) reported their findings on aza-arenes in cigarette MS.

The listing of single delivery values rather than a range for dibenz[*a,h*]acridine (0.1 ng/cigt) and 7*H*-dibenzo[*c,g*]carbazole (0.7 ng/cigt) indicates the MS levels cited are those reported from a single study, which appears to be that of Van Duuren *et al.* (1960a, 1960b). Wynder and Hoffmann (1964, 1967) cited their own *unpublished* 1963 findings (Candeli *et al.*, 1963) that they could not detect dibenz[*a,h*]acridine in cigarette MS. These findings have never been published in a peer-reviewed journal. The delivery level of 10 ng/cigt for dibenz[*a,j*]-acridine was discussed by Wynder and Hoffmann (1964, 1967). It was the unpublished 1963 finding of Candeli, Hoffmann, and Wynder (1963). Thus, the upper limit (10 ng/cigt) of the range for MS delivery of dibenz[*a,j*]acridine is that reported by Hoffmann, co-author of the 1990 "List of 43."

Single MS values for dibenz[*a,h*]acridine and 7*H*-dibenzo[*c,g*]carbazole in MS based on a cigarette manufactured in 1959-1960 or 1963 are hardly representative of more recently manufactured cigarettes. It is well recognized that a variety of cigarette design technologies [efficient filtration, filter-tip additives, processed tobacco materials (RTS, expanded tobaccos),

air dilution (porous paper, filter-tip perforations), and paper additives] has progressively reduced the sales-weighted average MS TPM by almost 70% from 40 mg/cigt in the early 1950s to less than 12 mg/cigt currently. At the same time that the reduction of delivery of MS TPM was accomplished; the composition of the MS was also altered. *E.g.*, for MS TPM, the BaP content — expressed as ng BaP/mg TPM — has decreased about 33% (from 1.2 ng/mg TPM to 0.8 ng/mg TPM) during the same time period. The 1979 Surgeon General's report (USPHS, 1979) summarizes the BaP data for a commercial cigarette sold in the USA from 1954 to 1979. In addition to changes in the composition of the MS TPM, changes in the composition of the MS vapor phase were also involved.

Nicotine and the tobacco proteins and amino acids are proposed as the major precursors of aza-arenes, including the aza-arenes in the "Lists of 43." (Chortyk and Schlotzhauer, 1973). Thus, the decrease in cigarette nicotine content and delivery since 1960 should certainly influence the pyrogenesis of the dibenzacridines and dibenzocarbazole during the tobacco smoking process. The levels of nicotine in US cigarette tobacco blends (and MS) decreased on average more than 40% between 1960 and 1988.

In addition, inconsistencies among numerous isolation studies raise serious questions about the actual presence of these three aza-arenes in the MS (or SS) from cigarettes manufactured after the mid-1960s. Results from German, Japanese, and American groups of investigators on their search for dibenz[*a,h*]acridine (I), dibenz[*a,j*]acridine (II), and 7*H*-dibenzo[*c,g*]carbazole (III) in MS CSC and/or nicotine pyrolysates are summarized in **Table 12.** Only Van Duuren *et al.* (1960a, 1960b) in their published report and Candeli *et al.* (1963) in their unpublished report have detected any of these three aza-arenes in cigarette MS!

Examination of the results summarized in **Table 12** indicates that Van Duuren *et al.* (1960a, 1960b) reported the identification of the three aza-arenes in MS CSC and two of them (I and II) in a nicotine pyrolysate. However, Candeli *et al.* (1963) failed to identify I but did identify II in MS CSC. The Candeli *et al.* findings reported in 1963 on II in MS CSC were not confirmed in 1979 by investigators from the *same* laboratory (Schmeltz *et al.*, 1979). Two later studies (Schmeltz *et al.*, 1972, 1979) confirmed the 1960 finding by Van Duuren *et al.* that 7*H*-dibenzo[*c,g*]carbazole was not present in a nicotine pyrolysate.

Examination of the detailed chromatograms presented in a more recent study on aza-arenes in MS and SS by Grimmer *et al.* (1986, 1987) indicates the presence of several benzacridines (benz[*a*]acridine, benz[*c*]acridine). However, no gas chromatographic peaks corresponding to standard dibenz[*a,h*]acridine and dibenz[*a,j*]acridine peaks are visible in the chromatograms of the aza-arene fraction from either the cigarette MS or SS.

The failures by numerous research groups (**Table 12**) to detect the two dibenzacridines, I and II, in tobacco smoke cannot be attributed to difficulties or problems in the analytical procedures. Motohashi *et al.* (1993) reviewed the analytical procedures that enabled investigators to identify several benzacridines and their homologs plus dibenz[*a,h*]acridine and dibenz[*a,j*]-acridine in a variety of environmental samples (urban air; gasoline engine exhaust; Diesel engine

TABLE 12: DIBENZ[*a,h*]ACRIDINE, DIBENZ[*a,j*]ACRIDINE, AND 7*H*-DIBENZO[*c,g*]CARBAZOLE IN NICOTINE PYROLYSATES (PYR) AND MAINSTREAM CIGARETTE SMOKE CONDENSATE (CSC)

	Dibenz[*a,h*]acridine, I		Dibenz[*a,j*]acridine, II		7*H*-Dibenzo[*c,g*]carbazole, III	
Investigators	Pyr	CSC	Pyr	CSC	Pyr	CSC
Van Duuren *et al.* (1960a, 1960b)	yes[a]	yes	yes	yes	no	yes
Candeli *et al.* (1963)	NE	no	NE	yes	NE	NE
Kaburaki *et al.* (1970)	no	NE	no	NE	NE	NE
Schmeltz *et al.* (1972)	no	NE	no	NE	no	NE
Schmeltz *et al.* (1979)[b]	no	no	no	no	no	no
Snook (1978)	NE	no	NE	no	NE	no
Snook *et al.* (1981)	NE	no	NE	no	NE	no
Grimmer *et al.* (1986, 1987)	NE	no	NE	no	NE	no
Kamata *et al.* (1992)	NE	no	NE	no	NE	NE

[a] yes = compound identified; no = compound not found or identified; NE = substrate not studied or not examined for compound in question.

[b] Study with radiolabeled nicotine.

exhaust; street dust; sediment from lake, river, and salt-water sources). Motohashi *et al.* (1993) also reviewed in some detail the reports by Schmeltz *et al.* (1972(, Snook *et al.*, Grimmer *et al.* (1987), and Kamata *et al.* (1992) on the identification of various benzacridines in tobacco smoke, but they did not mention the reported identification of dibenz[*a,h*]acridine and dibenz-[*a,j*]acridine in MS by Van Duuren *et al.* (1960a, 1960b).

In view of the conflicting evidence on the presence and/or level in cigarette MS (or SS) of these three aza-arenes (I, II, and III), it appears presumptuous to include dibenz[*a,h*]acridine, dibenz[*a,j*]acridine, and 7*H*-dibenzo[*c,g*]carbazole in the two "Lists of 43."

An explanation of the difference in results concerning the presence or absence of these three compounds in MS CSC may be the difference between cigarettes made in the early 1960s *vs* those made more recently. However, there does not appear to be a logical explanation for the difference in the results on these three aza-arenes (presence or absence) in a nicotine pyrolysate prepared in 1960 *vs* nicotine pyrolysates prepared in 1970, 1972, and 1979.

In summary, the situation with regard to the four aza-arenes considered to be significant "tumorigens" in tobacco smoke by OSHA (1994) and/or EPA (the 1990 Hoffmann-Hecht list) is as follows:

- OSHA did not list quinoline as a significant tumorigen whereas EPA did.

- Only one laboratory has reported the presence of the other three aza-arenes (dibenz[*a,h*]acridine, dibenz[*a,j*]acridine, 7*H*-dibenzo[*c,g*]carbazole) listed in **Table 4** as tumorigens in tobacco smoke.

- One other laboratory reported the presence of dibenz[*a,j*]acridine in MS but not the other two aza-arenes. However, its findings have never been peer reviewed.

- In comparable tumorigenicity studies, the aza-arenes are much less tumorigenic to mouse skin than their corresponding PAH analogs and much less tumorigenic than BaP.

- Failure to detect the three aza-arenes dibenz[*a,h*]acridine, dibenz[*a,j*]acridine, and 7*H*-dibenzo[*c,g*]carbazole in cigarette MS and/or in nicotine pyrolysates was reported in at least seven studies conducted periodically between 1970 and 1992.

- The levels in MS of the three aza-arenes listed by OSHA and EPA, if they are present at all in MS, are much less than that of BaP.

N-Nitrosamines (NNAs)

Hoffmann and Hecht (1990) do not acknowledge that the MS levels listed for both the volatile *N*-nitrosamines (VNAs) and the tobacco-specific *N*-nitrosamines (TSNAs) may be incorrect (and high) because of the artifactual formation of both types of NNAs during MS (and SS) collection for analysis as reported by Caldwell and Conner (1989, 1990). The EPA and OSHA apparently accepted without question the MS VNA and MS TSNA levels tabulated by Hoffmann and Hecht (1990) and cited by the Surgeon General in his 1989 report (USPHS, 1989).

The artifactual formation of NNAs during the collection and analysis of MS and SS has been noted many times over the years. Neurath *et al.* (1965) were one of the earliest group of investigators to discuss this problem. More recently, Brunnemann *et al.* (1977), from their study of the levels of NNAs in MS and SS, reported lower levels than previously reported for VNAs in MS, attributing the lower levels to the avoidance of artifactual formation of NNAs during smoke collection and analysis. They wrote:

> In fact, several of the cigarettes which were machine smoked earlier and analyzed without precautions, when smoked by us under the same conditions but with precautions, yielded 25 to 100% lower values for DMN [*N*-nitrosodimethylamine] and NPY [*N*-nitrosopyrrolidine] for the mainstream smoke...
>
> The nitrate content of the tobacco appears to be a determining factor for the concentration of volatile nitrosamines in the smoke. Selective removal of these nitrosamines does occur with cellulose acetate filter tips but not with charcoal filter tips.

Guerin *et al.* (1992) in their review of NNAs in ETS comment on four ETS-related

studies, those of Brunnemann *et al.* (1978), Stehlik *et al.* (1982), Matsushita and Mori (1984), and Klus *et al.* (1987). They summarized the results on the determination of NNAs in natural and artificial ETS-environments as follows:

> [T]he concentration of nitrosodimethylamine in commonly encountered ETS-contaminated indoor air is likely to range from < 10-40 ng/m³. Nitrosodiethylamine and nitrosopyrrolidine are likely to be present at similar but lower concentrations. Extrapolating from studies of artificial environments suggest [*sic*] NNN and NNK concentrations in common environments will range from < 1-1 ng/m³.

They also noted that occasionally, NDMA concentrations may show excursions to 100 ng/m³.

It was noted previously (**Table 6**) that many of the claims about the PAHs in tobacco smoke, particularly those demonstrated to be tumorigenic to the skin of rodents, were subsequently demonstrated to be either incorrect or equivocal. The number of points of contention about the NNAs in tobacco smoke are much fewer than the number listed for the tobacco smoke PAHs and are tabulated in **Table 13.**

TABLE 13: *N*-NITROSAMINES IN TOBACCO SMOKE

Abbreviations: PAH = polycyclic aromatic hydrocarbon; NNA = *N*-nitrosamine; VNA = volatile *N*-nitrosamine; TSNA = tobacco-specific *N*-nitrosamine; NNN = *N'*-nitrosonornicotine; NNK = 4-(*N*-methylnitrosamino)-1-(3-pyridinyl)-1-butanone; NAB = *N'*-nitrosoanabasine; NDMA = *N*-nitrosodimethylamine; NDEA = *N*-nitrosodiethylamine; NPYR = *N*-nitrosopyrrolidine; MS = mainstream smoke; BaP = benzo[*a*]pyrene; CSC = cigarette smoke condensate

Proposal	*Contradiction*
§ Conditions are appropriate (presence of nitrogen oxides, water, and secondary amines, pH < 7.0) in a burning cigarette for the pyrogenesis of NNAs such as NDMA (Druckrey and Preussmann, 1962). Because of the presence in tobacco smoke of the secondary nicotine-related amines nornicotine and anabasine, nitrogen oxides, and water, it is highly likely that NNN and NAB will be formed in tobacco smoke (Boyland *et al.*, 1964a, 1964b, 1964c)	
§ Serfontein and Hurter (1964, 1966) reported the identification of NNAs in cigarette MS.	§ First claims (Serfontein and Hurter, 1964, 1966) of identification of NNAs in cigarette MS were challenged with counterclaims that NNAs were artifactually produced during smoke generation, collection, and analysis (*cf.* Neurath *et al.*, 1964). Neurath *et al.* (1964) reported the presence of an NNA but subsequently discovered the identified compound was produced artifactually during the smoke processing.
§ Since NNAs volatile and tobacco-specific) occur in tobacco, a part of the NNAs in cigarette MS is a result of direct transfer of the NNAs from tobacco to smoke, the remainder results from formation and	§ The premise of the pyrogenesis of NNN and NNK during the cigarette smoking process has been challenged by Fischer *et al.* (1990b, 1991a) who reported that these compounds occur in cigarette MS

Table 13: Continued

Proposal	*Contradiction*
Continued:	*Continued:*
transport during the smoking process (Adams *et al.*, 1983). For NNK, the transfer from tobacco to smoke ranges from 6.9 to 11.0% of the amount in the tobacco; this represents about 30% of the NNK in MS. The remainder in MS is formed during the smoking process (Hoffmann *et al.*, 1976b; Hecht *et al.*, 1978a).	only by transfer from the tobacco rod.
§ The problem of artifactual formation of NNAs has persisted from the mid-1960s to the present (Neurath *et al.*, 1964; Fredrickson, 1965/1967; Krull *et al.*, 1978; Eisenbrand *et al.*, 1983; Caldwell and Conner, 1989, 1990). Continual improvement in smoke collection and analytical procedures has progressively reduced the analytical error.	
§ TSNAs in CSC have little or no influence on the host response in skin-painting studies. Little of the VNAs remain in the CSC after collection and preparation for the skin-painting bioassay. The only NNAs to consistently elicit a positive response at the application site in skin-painting studies are the alkyl-*N*-nitrosourethanes, none of which has been identified in tobacco or tobacco smoke to date. Hundreds of rodent skin-painting studies with CSC and its fractions have been conducted since the first successful production of carcinoma in mice painted with CSC (Wynder and Hoffmann, 1964, 1967 and references cited; Gori, 1976a, 1976b, 1977, 1980; NCI, 1980). Even in the massive NCI-TWG decade-long study, no attempt was made to correlate NNA content with bioassay results. It was assumed from studies with individual NNAs that they had little if any influence on CSC tumorigenicity to mouse skin. Millions of dollars and thousands of hours have been expended since 1953 in conducting bioassays — particularly mouse skin-painting studies — that do not adequately define the total tumorigenicity of CSC in laboratory animals.	
§ Precursors of NNAs in both tobacco and tobacco smoke are the proteins and amino acids (plus nitrate) for the VNAs (Brunnemann *et al.*, 1983a, 1983b; Hoffmann *et al.*, 1984a) and nicotine and nicotine-related alkaloids (plus nitrate) for the TSNAs (Boyland *et al.*, 1964a, 1964b, 1964c; Rathkamp *et al.*, 1973; Hecht *et al.*, 1976a, 1977a). The levels of NNAs in tobacco and its smoke parallel the tobacco nitrate level (Morie and Sloan, 1973; Hecht *et al.*,	

Table 13: Continued

Proposal	*Contradiction*
Continued:	
1974a, 1975b; Tso *et al.*, 1975).	
§ Removal of lipophilic PAH precursors from tobacco by solvent extraction reduces the PAH level in MS and the tumorigenicity (mouse skin-painting) of the CSC (Wynder, 1956; Wright, 1957a; Wynder *et al.*, 1958a, 1958b, 1959). *This led to their recommendations to remove the lipophilic components from tobacco.* Confirmation of the reduced levels of PAHs in MS from cigarettes fabricated with organic solvent-extracted tobaccos was provided by Rodgman and Cook (1965).	§ Personnel from Wynder's laboratory subsequently *recommended the addition of lipophilic compounds (*e.g., n-*hentriacontane) to tobacco* (Brunnemann and Hoffmann, 1982) to reduce the generation during the smoking process of nitrate-derived nitrogen oxide which was postulated as a reactant in the formation of NNAs.
Eventually, personnel from Wynder's laboratory *recommended the addition of lipophilic compounds (*e.g., n-*hentriacontane) to tobacco* (Brunnemann and Hoffmann, 1982) to offset the effect of nitrate-derived nitrogen oxides in the formation of NNAs. The biological activity of the CSC from extracted tobacco was reduced but to a much lesser extent than the PAH (and BaP) decrease.	
§ NNA formation in tobacco smoke involves the reaction of methyl nitrite and secondary amines (Rodgman, 1960; Rodgman and Cook, 1965; Wynder and Hoffmann, 1967).	§ The proposal (Rodgman, 1960; Wynder and Hoffmann, 1967) that NNAs arise by reaction of methyl nitrite with secondary amines was shown to be invalid: Methyl nitrite in MS is zero initially but during the period of tobacco smoke generation, collection, and analysis it is formed artifactually in tobacco smoke (Vilcins and Lephardt, 1974a, 1974b).
§ NNA formation in tobacco smoke involves reaction among secondary amines, nitrogen oxides, and water.	
§ Despite the contradictory evidence that precludes the involvement of NNAs either collectively or individually not only in various bioassays with laboratory animals but also in respiratory tract cancer in cigarette smokers, some investigators still maintain that the "tumorigenicity" of cigarette smoke in humans is due to its PAH content and its content of at least one TSNA, NNK.	§ Individual NNAs, particularly the TSNAs, have little or no influence on CSC tumorigenicity in the skin-painting bioassay. Millions of dollars and thousands of hours have been expended since 1953 in conducting bioassays that do not adequately define the total tumorigenicity of CSC in laboratory animals.
As recently as 1991, Hecht and Hoffmann (1991b) wrote: "[P]olynuclear aromatic hydrocarbons and NNK [4-(*N*-methylnitrosamino)-1-(3-pyridyl)-1-butanone] are the major carcinogens involved in lung cancer induction by cigarette smoke..."	Inhalation studies with NNAs at levels comparable to those in cigarette MS have consistently been negative.
	Lung tumor production by exposure to extremely high inhalation levels of NNAs was classified as

Table 13: Continued

Proposal	*Contradiction*
Continued:	*Continued:*
Hoffmann and Hecht (1990) also noted that NNK had not been tested in laboratory animals for tumorigenicity via inhalation.	"equivocal" by the RTECS (RTECS, 1987). Bioassay results in life-time inhalation studies with laboratory animals exposed to various cigarette MSs show no relationship between tumor production and NNA content (VNAs and/or TSNAs).
§ On the basis of the following results, nitrate *addition* or use of *high*-nitrate tobaccos was proposed: Addition of nitrate to the tobacco blend significantly reduces the MS delivery levels of "tar", PAHs, and phenols. The odd-electron compound nitric oxide generated from nitrate during the smoking process interrupts the free-radical mechanism of formation of PAHs (Hoffmann and Wynder, 1967, 1968). The tumorigenicity (% tumor-bearing animals) of the resulting cigarette smoke condensate is also reduced.	§ *Later, data showed that increasing the nitrate increases both the VNAs and TSNAs in MS.* Even though an increased level of TSNAs in MS CSC was accompanied by decreased tumorigenicity of the CSC to mouse skin, it was subsequently proposed to *remove* nitrates from the tobacco or use *low*-nitrate tobaccos (Brunnemann and Hoffmann, 1982). However, Hoffmann and Hecht (1990) eventually included several of the NNAs and TSNAs in their list of "tumorigenic agents in tobacco and tobacco smoke."
§ No VNA is considered a "marker" for other VNAs in MS; no TSNA is considered a meaningful "marker" for other TSNAs, either individual or total, in MS. No NNA — either TSNA, VNA, or nonvolatile NA — is considered a "marker" for the tumorigenicity of CSC in the mouse skin-painting assay.	§ As noted previously, as the level of nitrate in tobacco and subsequently the levels of the TSNAs in CSC increase, the tumorigenicity of CSC to mouse skin decreases (Wynder and Hoffmann, 1967; Hoffmann and Wynder, 1972a, 1972b) but its mutagenicity in the Ames system (*Salmonella typhimurium*) increases (Mizusaki *et al.*, 1977b).
§ The tumorigenicity of NNAs is inhibited by a variety of tobacco smoke components. *E.g.*, *D*-limonene is anticarcinogenic to NNK (Wattenberg and Coccia, 1991); the alcohols ethanol, *n*-butanol, and *tert*-butanol are anticarcinogenic to NNN (Waddell and Marlowe, 1983); indole (Matsumoto M *et al.*, 1977), cholesterol (Cohen *et al.*, 1982), β-sitosterol (Wattenberg, 1981), 3,4,5-trihydroxy-benzoic acid (gallic acid) (Mirvish *et al.*, 1975) and its esters (Lo and Stich, 1978; Teel and Castonguay, 1992) are anticarcinogenic to several of the NNAs in tobacco smoke (*cf.* Rodgman, 1991, 1992). Tobacco smoke not only contains other compounds [long-chained fatty acids (Takeda *et al.*, 1991)] reported to diminish the tumorigenicity of various NNAs but	